NEW DOPAMINE AGONISTS AND HYPERPROLACTINAEMIA

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NEW DOPAMINE AGONISTS AND HYPERPROLACTINAEMIA

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Aan Ellen

Quand on n'a que l'amour.....

aan mijn ouders

CONTENTS

CHAPTER 1

INTRODUCTION

History

After the first indication for the presence of lactogenic activity in pituitary extracts was demonstrated by Stricker and Grueter in 1928, Riddle et al. (1933) gave the name prolactin to the substance responsible for this activity.
The same effect was shown in the experiments on the sheep's pituitary by White et al. (1937). It was only in 1963 that it became clear (Riddle et al.) that prolactin, as well as the stimulating influence on milkproduction by the mammae, had a wide array of effects on different organs. Nicoll and Bern in their review article (1972) gave a summary of the multiple effects of prolactin in different species from reptiles to vertebrates, not yet including mankind (table 1). The presence of prolactin in man had been supposed, but could not been demonstrated with certainty. This is in part due to the fact that growth hormone (isolated from humans by Chadwick et al. in 1961) possesses a relatively strong lactogenic activity and is produced in large quantities from the anterior pituitary. In the early bio-assays of the nineteensixties, the lactogenic activity of growth hormone was measured and could not be separated from a possible contribution of prolactin. It was to take approximately 10 years from 1961 before the existence of human prolactin was proven, despite the experiments of Pasteels in 1963, which showed prolactin producing cells in the human anterior pituitary. Frantz et al. (1972a) identified prolactin as a separate protein. In their in vitro studies the lactogenic activity in human serum was inhibited by an anti-serum directed against sheep's prolactin, but not by an anti-serum against growth hormone.
Finally, however, Friesen et al. (1970) undeniably proved in the monkey and in humans that prolactin is a separate entity next to growth hormone. Hereafter prolactin was isolated in sufficient quantities (Hwang et al. 1971, Lewis et al. 1971, Friesen et al. 1972) and the development of a specific radioimmunoassay followed rapidly.

Molecular structure

Human prolactin consists of a simple protein-chain of 198 aminoacids linked by three disulfide bridges which are a typical feature of the prolactin molecule (Shome and Parlow 1977). The similarity with growth hormone (hGH) and placental lactogen (hPL) is present only for 16% and 13% respectively, which is remarkable in view of their strong lactogenic activity (figure 1).

Table 1 Summary of actions of prolactin

Actions of prolactin related to reproduction	Actions of prolactin involving growth promotion
Mammals	*Mammals*
Mammary development and lactation	Mammary development
Preputial gland size and activity	Sebaceous & preputial gland growth
Synergism with androgen on male sex accessory glands	Hair growth
	Erytropoietic
Luteotrophic	Renotrophic
Luteolytic action in rats and mice	Spermatogenic
Fertility in dwarf mice	Male sex accessory development
Increased testis cholesterol	Luteotrophic
Increased androgen binding in human prostate	Growth hormone like metabolic actions
Stimulation of gluceronidase activity in rodent testis	Effects on lipid deposition and/or mobilization reported in teleost, amphibians, reptiles, birds and mammals
Parental behaviour	
Decreased copulatory activity in male rabbits	
Advanced puberty in rats	
Vaginal mucification in rats	Hyperglycemic-diabetogenic action reported in amphibians, birds and mammals
Antiovulatory and antiluteinizing in rats	
Relaxation of uterine cervix in rats	
Reduced catabolism of progesterone by rat uterus	Effects on blood urea nitrogen (BUN) N balance, blood glucose, free fatty acid (FFA), and calcium metabolism in humans similar to HGH
Inhibition of myometrial contractions	
Increased estradiol binding by rat uterus	

Actions of prolactin involving water and electrolyte balance	Actions of prolactin involving synergism with steroid hormones or on organs also influenced by steroids
Mammals	*Mammals*
Lactation	Mammary growth (ovarian steroids)
Increased Na^+ retention at renal level	Milk secretion (corticosteroids)
Corticotropic	Sebaceous and preputial gland secretion (gonadal and cortical steroids)
Actions of prolactin on integumentary (Ectodermal) structures	Growth and secretion of male sex accessory glands (androgens)
	Luteotrophic action (estrogens?)
Mammals	Renal Na^+ reabsorption (aldosterone?)
Mammary development and lactation	and renotrophic (androgens)
Sebaceous and preputial gland size and activity	Spermatogenesis (androgens)
	Advanced puberty (gonadal steroids)
Hair maturation	Hair growth (androgens, corticosteroids)
	Vaginal mucification in rats (estrogen and progesterone)

From Physiological actions of prolactin Handbook of Physiology Endocrinoloy Charles S Nicoll 1974 253

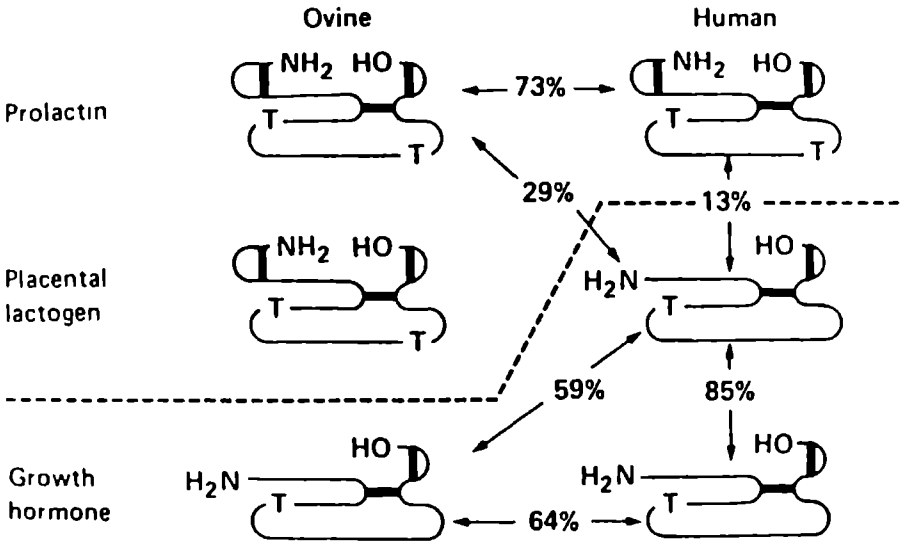

Figure 1 Comparisons between the structures of ovine and human prolactin, placental lactogen and growth hormone Diagrams indicate the positions of disulphide bonds (heavy bars) and of tryptophan residues (T) Figures indicated the percentages of identical amino acid pairs between hormones Gaps have been introduced into the sequences to maximize identity
From Hormonal control of lactation Monographs on Endocrinology Cowie A, Forsyth S Hart S 1980 21

Serum prolactin is apparent in three forms: small prolactin with a molecular weight of about 23,000 Dalton, big prolactin of 40,000-50,000 Dalton and big-big prolactin of more than 60,000 Dalton (Suh and Frantz 1974). The large molecules probably are formed by aggregation in the serum after excretion of small molecules by the pituitary. Nowadays serum prolactin is measured by specific and sensitive radioimmunoassays.

Physiology

Of all the pituitary hormones, prolactin seems to be the most versatile as it influences many physiological processes (Nicoll 1974, Leong et al. 1983). Its role in the lactogenesis and galactopoiesis is one of paramount importance in the life of the neonate and thus in the survival of the species.
The prolactin producing cell is named lactotropic cell, analogous to for instance, gonadotropic cells. Herlant and Pasteels (1967) identified the prolactin producing cell for the first time by means of the light-microscope and his findings were later confirmed by Pasteels (1972) with the help of immunocytochemical methods. In the hormone secretive pituitary 40-50% of all cells consist of lactotropic cells both in females and in males according to studies and calculations with

the use of immunocytochemical anti-sera and the 'reverse hemolytic plaque assay-technique' (Lugue et al. 1986). It is generally assumed that lactotropic cells are spread throughout the pituitary in clusters of 5 to 10 cells. Recently, Papka et al. (1986) showed that in the rat they are grouped in two zones, a thin peripheral layer and a more pronounced central layer.
With the 'reverse hemolytic plaque assay', Hymer et al. (1974) discovered a correlation between the size of the cell and the amount of prolactin secreted by it. With the help of this technique Neill et al. (1987) suggested the existence of two sorts of cells: one that produces a large quantity of prolactin and one that secretes a small quantity. The cells that secrete a larger quantity of prolactin would be more directly controlled by the hypothalamus whereas the smaller quantity producing cells would act more autonomously. Lactotropic cells of the peripheral layer are in general smaller and less under hypothalamic control compared to cells of the central layer. The latter are able, due to the size and hypothalamic regulation, to produce more prolactin (Boockfor and Frawley 1987). More investigation is required to clarify whether these differences in prolactin secretion are caused by extrinsic factors such as interaction with surrounding cells (Sato 1980) or by intrinsic factors such as stage of cell cycle (Snyder et al. 1978).

After Harvis' hypothesis that the pituitary is controlled by the hypothalamus (1955), similar suggestions were made regarding the regulation of prolactin. Everett (1954 and 1956) supposed the existence of a hypothalamic factor which would reach the anterior pituitary via the portal system, thus inhibiting prolactin secretion. He based his hypothesis on the observation of an increased prolactin secretion in the, from the hypothalamus isolated, pituitary. Pasteels (1963) additionally showed a decrease in prolactin secretion when hypothalamic extracts were added to the culture medium. Meites et al. (1963) confirmed the existence of a prolactin inhibiting factor (PIF) in these hypothalamic extracts. Macleod (1976) finally proved the presence of PIF as dopamine which in the hypothalamus, acts amongst others as neurotransmitter. This conclusion was reached after quantitative measurement of dopamine from the bloodvessels in the stem of the pituitary, disregarding the large contribution of dopamine from the posterior pituitary via the short portal circulation (Ben-Jonathan 1980). By the demonstration of the presence of dopamine receptors on the lactotropic cell membranes, Goldsmith et al. (1979) confirmed that on cellular level prolactin secreting cells are (in part) regulated by dopamine.

One had hypophesized the existence of prolactin inhibiting factors other than dopamine for a long time. Gamma Amino Butyric-Acid (GABA) (Enjalbert et al. 1979) and Gonadotropin releasing hormone Associated Peptide (GAP) (Nikolics et al. 1985) have been mentioned, but until now no definite proof has been given for their role in the regulation of prolactin secretion.

Nipple stimulation, in particular during the puerperium, gives rise to strong prolactin secretion (Neill 1974). Acute stress has the same effect, although to a lesser extent (Neill 1970). This is despite the fact that there is no clear evidence for the existence of a separate prolactin releasing hormone. After two minutes of nipple stimulation there is already a marked increase in serum prolactin concentration. An obvious explanation for this neurogenic stimulation would be dehibition of hypothalamic influence, resulting in an immediate decrease in dopamine secretion (Chiocchio et al. 1979). However, the decrease of dopamine concentration measured in the portal blood circulation after nipple stimulation has been found too small to explain the increase in prolactin secretion (Plotsky and Neill 1982). Hypothalamic dopamine secretion has even appeared to be rather insensitive to prolactin increasing stimuli such as suckling (de Greef et al. 1981).A more convincing argument in support of a prolactin releasing factor is the fact that removal of the posterior pituitary counteracts the increase of prolactin after suckling without changing basic prolactin concentrations (Murai and Ben-Jonathan 1987). Other substances can be demonstrated in the portal system such as thyreotrope releasing hormone (TRH) (Leong and Neill 1987), vaso-active intestinal peptides (VIP) (Abe et al. 1985) and oxytocin (Samson et al. 1986). Their concentrations change little after nipple stimulation and they therefore seem not responsible for the increase in prolactin secretion.
Many neuropeptides, amongst others serotonin and several endorphins seem to play a role in the hormonal regulation of production and secretion of prolactin and gonadotropins. A prolactin releasing factor, however, has not been recognized and described as yet. Murai and Ben-Jonathan (1987) suggested that such a substance would derive from or be mediated by the neurosecretive pituitary.
Next to the regulation of prolactin secretion by the hypothalamus, paracrine and autocrine mechanisms are also possible. VIP can be synthesized in the lactotropic cell (Arnaout et al. 1986); it stimulates prolactin secretion. It is possible that dopamine counteracts the effects of VIP or inhibits the secretion of VIP; in this field more research is necessary. Aguilera et al. (1982) found that angiotensine 2 is also able to enhance prolactin secretion by the lactotropic cell. It is being synthesized by gonadotropic cells after GnRH stimulation (Denef et al. 1986). Physiological consequences of these paracrine regulations are not clear as yet, but they may play a role in the more chronic changes of prolactin secretion such as found after, for instance, oestrogen stimulation.

One can conclude that the lactotropic cell is responsible for the synthesis, storage and secretion of prolactin (Farquhar et al. 1975). The synthesis and secretion are influenced by TRH, VIP as well as dopamine via the same second messengers such as cyclic AMP, calcium and some phosphoinositides. The receptors for TRH, VIP and dopamine are all membrane-bound (Murodoch et al. 1985). Dopamine exerts its action mainly by inhibiting cyclic AMP (Swennen and Denef 1982), whereas VIP stimulates the production of cyclic AMP (Nagy et al. 1987). On the other hand, TRH acts via calcium and phosphoinositides (Martin 1985).

These autocrine, paracrine and endocrine regulation systems collaborate harmoniously in their control by influencing the synthesis, storage and secretion of prolactin.

PATHOLOGY

Most substances which cause a hyperprolactinaemia inhibit dopamine synthesis or block dopamine-receptors on hypothalamic or pituitary level (Frantz et al. 1972a, Benmont et al. 1974, Gold et al. 1977, Carlson and Ippoliti 1977, Masala et al. 1980, del Pozo and Köbberling 1981). The reverse, hypoprolactinaemia seems to be non-existent as well in clinical experience as in the literature. One has suggested (Schulz et al. 1976, del Pozo et al. 1979) that hypoprolactinaemia would also give rise to an insufficient luteal phase, but this has never been confirmed. In contrast, hyperprolactinaemia is found frequently and the incidence given in the literature varies between 11% and 47% with a mean of 24,2% in women with secondary amenorrhoea (Flückiger et al. 1981; table 2). It was

Table 2 Incidence of hyperprolactinaemia in secondary amenorrhoea

Reference	No of Patients	Hyperprolactinemia (%)	Galactorrhea as % of hyperprolactinemia
Franks et al (1975)	40	20	35
Seppala et al (1975)	34	47	53
Canales et al (1976a)	116	28	0
Bohnet et al (1976)	127	13	53
Jurgensen et al (1976)	305	11	-
Rjosk et al (1976)	445	16	89
Bergh et al (1977)	287	15	87
Seppala et al (1977)	123	33	38
Shearman and Fraser (1977)	90	39	83
Leyendecker et al (1977)	50	24	66
Lunenfeld et al (1980)	352	21	52
	Σ1969		
Mean and range	24 2(11-47)		55 5(0/35-89)

From Prolactin Physiology, Pharmacology and Clinical Findings Monographs on Endocrinology Fluckiger E, del Pozo E, von Werder K 1982,118

initially thought that hyperprolactinaemia could be recognized in the galactorrhoea/amenorrhoea syndromes, of which the most well known is the Chiari-Frommel syndrome described in 1855 (Chiari et al. 1855). Pathognomonic is the persistence of postpartum lactation together with amenorrhoea. Frommel described the syndrome again and he added more clinical data (Frommel 1882). Argonz and del Castillo (1953) mentioned the same syndrome though unrelated

to pregnancy. In the description of this syndrome by Forbes et al. (1954), the frequent incidence of pituitary tumours was noted. At present it is clear that in a case of galactorrhoea with amenorrhoea, hyperprolactinaemia is a very probable cause. However, not all patients with hyperprolactinaemia show galactorrhoea. Changes in the menstrual cycle appear to be a more sensitive parameter than galactorrhoea as a symptom of hyperprolactinaemia (Seppälä et al. 1977). Hyperprolactinaemia can be triggered by the use of drugs but it can also be found in some forms of hypothyroidism (Samaan et al. 1977, Yamamoto et al. 1983). It is well known that TRH has a prolactin stimulating action and in the case of primary hypothyroidism one can expect a minor or moderate degree of hyperprolactinaemia. A long standing exposure to oestrogens can also give rise to a mild hyperprolactinaemia by a direct influence on lactotropic cells (Frantz et al. 1972b). This, of course is only true for exogenous oestrogens as otherwise hyperprolactinaemia would give a hypogonadotropic status. In most of the cases there is no clear cause for the hyperprolactinaemia (see table 3). In many instances there is a tumorous growth of prolactin producing cells in the pituitary which could produce a so called micro- or macro-adenoma (Thorner 1977, von Werder and Rjosk 1979). It remains unclear which is cause and which is consequence: with a continuous malfunctioning of these cells by insufficient

Table 3 Causes of elevated serum prolactin concentrations

Physiological
Pregnancy and post partum
Pathological
Hypothalamic lesions (traumatic, inflammatory and neoplastic hypothalamic disorders)
Stalk section
PRL-secreting pituitary tumours
Non PRL-secreting tumours impinging upon the pituitary stalk
Hypothyroidism
Hypo-hypercortisolism
Chronic renal failure
Liver cirrhosis
Chronic infiltrative processes of the mammary gland and the chest
Idiopathic
Pharmacological
Antagonists of dopamine neurotransmission
Agonists of serotonin neurotransmission
Antagonists of histamine H_2 receptors
Opiates
Sex steroids

From Pathophysiology of hyperprolactinaemic states Müller F In Gynecological Endocrinology Genazzani A, Volpe A, Facchinetti F (eds), 1987,214

inhibition (due to a shortage of PIF or PIF insensitivity of the cells) a hypertrophia or formation of an adenoma is possible.
Other endocrine disregulations can be present, dependent on the increase of serum prolactin concentration. In general the FSH value is normal or slightly raised, whilst LH concentration is low-normal or even decreased with a slowly diminishing pulsatile excretion. As a result follicles will not mature and steroid production by the ovary will gradually stop, eventually leading to a hypo-oestrogenic status.
A mild hyperprolactinaemia will rather cause an insufficient luteal phase, but later anovulatory cycles can occur and eventually with a sufficient rise in prolactin concentration, secondary amenorrhoea. The influence of hyperprolactinaemia in androgen metabolism is not clear: in the literature a mild increase of DHEAS is often mentioned but is not a consistent finding (Carter et al. 1977; Turpin et al. 1979). A summary of effects on inappropiately increased prolactin secretion is given in table 4.

Table 4. Effects on inappropriately increased prolactin secretion

Females	
Clinical	Failure to enter menarche
	Galactorrhoea with ovulatory cycles
	Short luteal phase
	Menomethorrhagia
	Anovulatory cycles
	Amenorrhoea[a]
	Hirsutism
Biochemical	Elevated plasma PRL concentrations
	Lack of sleep-related PRL elevations
	Absence of LH pulsatility
	Lack of positive estrogen feedback on LH
	Low basal estrogens[b]
	Elevated androgenic adrenal steroids
	Positive pituitary and ovarian response to exogenous stimulation
	Clomiphene resistance
Males	
Clinical	Failure to enter puberty
	Galactorrhoeac
	Oligoapermia, subfertility
	Signs of androgen failure
Biochemical	Elevated plasma PRL concentrations
	Lack of PRL elevations during sleep
	Low androgen production
	Positive pituitary and testicular response to exogenous stimulation

[a]Not necessarily associated with galactorrhoea
[b]Subjected to variance: Normal basal estrogens with normal or even elevated FSH are not uncommon
[c]Less frequent in males probably due to reduced mammary tissue mass.

From Prolactin Physiology, Pharmacology and Clinical Findings Monographs on Endocrinology Flückiger E, del Pozo E, von Werder K 1982,124

TREATMENT

When hyperprolactinaemia is diagnosed and treatment considered, this can be surgical (Derome et al 1979) or medical (Thorner 1977) or a combination of both (Landolt et al 1979) Initially radiation has been used (such as iridium implantation) (Kelly et al 1978), but this method is almost obsolete (Samaan et al 1979, Besser et al 1977)

There is a decreasing tendency towards surgical therapy the procedure is extremely tedious and there is a large chance of reoccurrence (Derome et al 1979) Although there is still discussion about the right policy in case of a macro-prolactinoma, it is generally accepted that a micro-adenoma or a hyperprolactinaemia without a tumour should be treated medically

Even before the discovery of human prolactin, experiments had started with the dopamine-agonist bromocriptine (figure 2), which, as appeared later, is bound specifically to dopamine receptors of the lactotropic cell and blocks the secretion of prolactin Subsequently synthesis also stops With hyperprolactinaemia, a dosage of 5 to 7 5 mg of bromocriptine (Parlodel^{R}) is generally sufficient The dosage is increased stepwise until the effect is reached

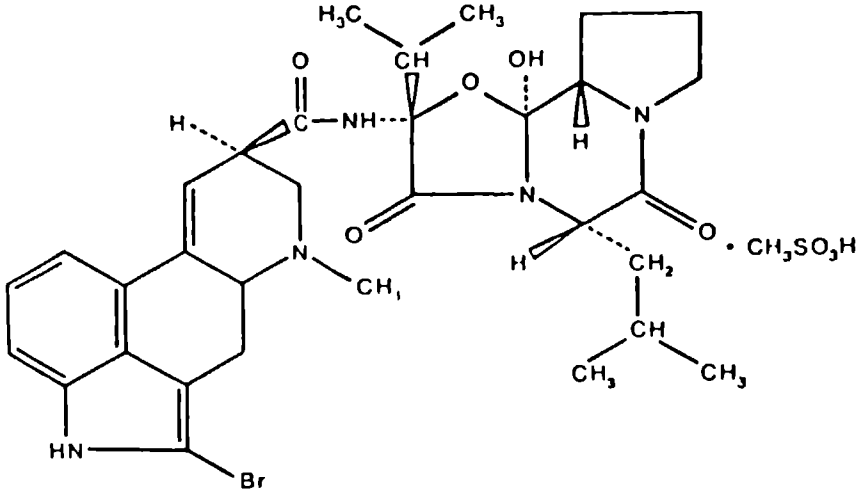

Figure 2 Structural formula of bromocriptine

Since the introduction of bromocriptine, its potent prolactin reducing ability has been confirmed in many publications In gynaecological patients this drug is especially prescribed in case of menstrual cycle disturbances with or without the desire of pregnancy Due to its dopaminergic effects, the administration of bromocriptine can give rise to side effects in certain sensitive subjects These

consist of nausea, dizziness, vomiting and orthostatic hypotension, but they are mostly dose dependent and temporary.

The safety of bromocriptine has been proven in many studies (Vance et al. 1984). Teratogenic effects have not been observed neither in animal experiments nor in pregnancies originated during bromocriptine medication (Corenblum 1979, Turkalj et al. 1982, Krupp et al. 1984).

Even when bromocriptine is commenced in a low dosage and slowly increased to therapeutic values, many patients are still unable to tolerate this drug. Its rather short halflife time necessitates frequent administration which is a disadvantage with regard to compliance. In some publications it is even suggested that severe side effects can occur particularly during the puerperium, but the value of these observations can be argued (Iffy et al. 1986, Katz et al. 1985, Shukla et al. 1985, Kemperman and Zwanikken 1987). With this in mind, however, it was justified to look for new dopamine agonists with the same or better prolactin reducing effect, but with less side effects and with a need of less frequent administrations to improve compliance. In view of the side effects of bromocriptine, which for the largest part are due to its alkaloid molecular structure, one has aimed for dopamine agonists which are not derived from the ergot-alkaloids. In the following chapters the results of studies regarding efficacy, tolerance and safety of new dopamine agonists are being discussed.

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CHAPTER 2

PROLACTIN SUPPRESSANT EFFECT OF CQP 201-403, A NEW DOPAMINE AGONIST, IN HYPERPROLACTINAEMIC WOMEN

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Gynaecologic Endocrinology 1987,1 93

ABSTRACT

To meet the need for a dopamine agonist compound which would offer longer action and improved tolerability, CQP 201-403 has been developed CQP is a propyl-ergoline which has shown specific and strong 24 hr prolactin suppression in healthy volunteers at oral doses of 0 01 mg and higher In the study 24 hyperprolactinaemic women were given once daily doses of 0 01 mg, 0 02 mg or 0 03 mg CQP 201-403, or placebo for 7 days in a double-blind study to assess the prolactin suppressant action and tolerability of the compound

The results show dose dependent prolactin suppression following the initial CQP dose which was sustained in steady state, when a clear 24-hour action was seen Tolerability was good and no drug attributable changes in safety measures occurred On the basis of its facility to suppress prolactin at well tolerated once daily doses, CQP would offer an advantage over currently available drugs Long-term therapeutic studies in hyperprolactinaemia are therefore warranted

INTRODUCTION

Since the introduction of synthetic dopamine agonists such as bromocriptine (Parlodel®) in the early 1970's, these drugs have been used in a variety of diseases; for example, persistent hyperprolactinaemia (1), inhibition of puerperal lactation (2), acromegaly (3) and Parkinson's disease (4). Except for the indication of puerperal lactation inhibition, therapy is generally of long duration, since most of these diseases are permanent (5).

The half-life of bromocriptine is relatively short, and, especially if higher doses are necessary, the drug has to be taken several times throughout the day (6). Although Parlodel^{R} is generally well tolerated, in some instances it gives rise to poor tolerance at the beginning of treatment or to persistent side-effects which demand that treatment be discontinued. Hence there is a need for new dopamine agonists with specific prolactin-lowering effects, with a longer half-life and if

possible with an improved adverse reaction profile. CQP 201-403 (figure 1) is a new 8-amino-ergoline which has an extremely potent prolactin-lowering effect in animals (7) and also in healthy human volunteers (8). The aim of the study reported here was to define the optimal once daily dosage of CQP 201-403 and to assess safety and tolerance in hyperprolactinaemic female volunteers.

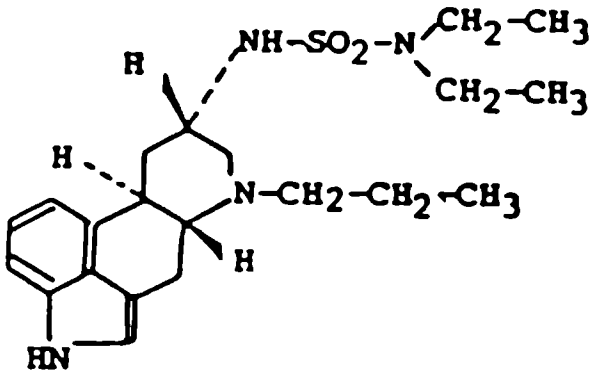

Figure 1. Structural formula of 8-amino-ergoline (CQP 201-403).

MATERIALS AND METHODS

Selection of volunteers

The study was conducted according to the Tokyo amendment of the Declaration of Helsinki (1975). After the protocol had been approved by the ethical committee of the university hospital, 24 women suffering from persistent hyperprolactinaemia (prolactin above 1200 mU /l) were invited to take part in the study. After receiving information concerning the trial, both by word of mouth and in written form, they all gave their signed consent to participate. Except for their hyperprolactinaemia, they were healthy women aged between 18 and 50 years. In women using Parlodel^{R}, the intake of this drug was stopped at least one month prior to the study. None of the women showed signs of a pituitary macroadenoma with extra-sellar extension.

Study design

The study was performed double-blind and placebo-controlled. The 24 patients were randomized and placed in one of three treatment groups receiving either 0.01 mg, 0.02 mg or 0.03 mg of CQP. In each group two of the eight women received placebo. The results from the six placebo-treated women were grouped together for statistical comparison with six women who received the drug in

each group. The duration of the study was seven days. Each group started the intake of CQP 201-403 or placebo at 9.00 hours on day 1. During this day (the acute phase of the study) the women remained at the clinic for assessment of vital signs and tolerance. On days 2 through 6 the women continued to take the capsules at home once daily after breakfast. On day 7 they again stayed in the clinic for assessment as on day 1, and returning for final measurement of safety parameters at 9.00 hours on day 8. If side-effects occurred at any time other than during the stays at the clinic visits the primary investigator was available by telephone. The women were routinely contacted by telephone on days 3 and 5 for enquiry concerning tolerance.

Protocol

During the week preceding the start of the study and on day 8 (24 hours after the last capsule intake) the following parameters were measured: ECG; complete urinalysis; hematology, consisting of hemoglobine, haematocrit, white cell count with differential and platelets; and blood chemistry, including minerals, bicarbonate, calcium, phosphorus, urea, uric acid, creatinine, glucose, total proteins and albumen, total bilirubin, triglycerides, cholestrol, alkaline phosphatase, LDH, ASAT, ALAT and CPK. All these parameters were measured by standard laboratory techniques.

Vital signs and hormone measurements

On day one, 1 hour before drug intake, at drug intake and ½, 1, 2, 6 and 8 hours thereafter, pulse rate, blood pressure (supine and standing), body temperature, respiratory rate, and weight were measured. These measurements were repeated on day 7, with additional measurements 10, 12, 23 and 24 hours after intake of the last capsule. Blood samples for assay of prolactin concentration were taken on day 1 immediately before capsule intake and 1, 2, 4, 6 and 8 hours thereafter. On day 7 blood was sampled at the same time intervals. In addition, samples were taken 1 hour before and 10, 12, 23 and 24 hours after intake. Serum prolactin concentrations were measured by a specific homologous DASP radioimmunoassay (9) with an intra-assay coefficient of variation of 6.3%. In addition to prolactin, FSH, LH, TSH, growth hormone and cortisol were measured by specific radioimmunoassay in the samples, employing a methodology previously described (9).

Analysis of results

All data collected were analyzed by means of descriptive statistics. According to treatment group mean, median standard deviation and minimum and maximum

values for each parameter were calculated. The six placebo-treated patients were pooled across cohorts for comparison with the six drug-treated women in each group. Prolactin values in the CQP treatment groups were compared with placebo values at individual time points using the Student t test for paired observations.

RESULTS

Prolactin

In figure 2 (left-hand panel) the prolactin levels obtained on day 1 (acute phase) are shown. All three groups receiving CQP 201-403 show a clear prolactin-lowering effect, which is most pronounced in the 0.03 mg treated group. On day 1 prolactin suppression in the 0.01 mg treated group was significantly different from the placebo-treated group from 2 hours after drug ingestion ($P < 0.05$).

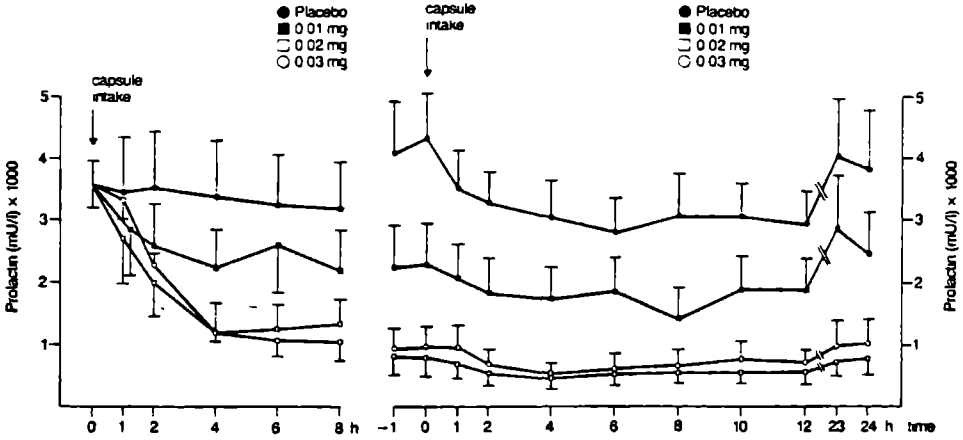

Figure 2. Mean (±SEM) serum prolactin concentrations on day 1: acute phase (left-hand panel); and mean (±SEM) serum concentrations on day 7: steady state (right-hand panel).

A similar pattern was seen in the 0.02 mg and 0.03 mg treated groups. At 8 hours the prolactin suppressant effect in these latter two groups was significantly greater than that seen in the lowest dose group ($P < 0.05$). The steady state prolactin concentrations obtained on day 7 are shown in the right-hand panel of figure 2. A clear difference is seen in all CQP 201-403 treated groups compared with the placebo group, with the strongest effect following the two higher doses. Results of the Student t test for paired observations applied to the data from hours 0, 6, 12 and 24 on day 7 compared with hour 0 (pretreatment) on day 1, show statistically significant prolactin reductions in all drug-treated groups ($P < 0.05$).

Vital signs

Body temperature, body weight and respiratory rate on days 1 or 7 showed no change which could have been treatment-related (data are not shown).
Figure 3 shows the changes in pulse rate in supine position and after 3 minutes standing, on day 1. The scatter within each group, especially in the upright values, is large (not shown); however, no systematic change in this parameter

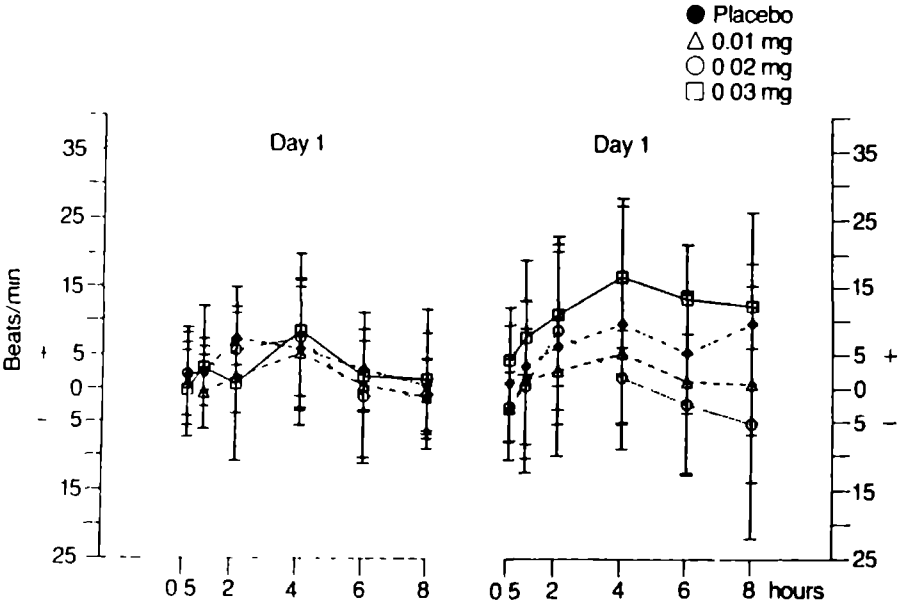

Figure 3. Radial pulse in supine position expressed as changes from baseline (left-hand panel); and radial pulse in standing position expressed as changes from baseline (right-hand panel). The data shown are mean values and 95% confidence limits of the three CQP 201-403 groups and the placebo group.

could be found in relation to drug intake. A similar pattern was seen on day 7 (data not shown). The few instances of transient pulse rate increases which were measured accompanied adverse reactions (see below). Figure 4 illustrates changes in blood pressure from baseline on day 1 in supine and standing positions. No marked changes were measured in any of the CQP 201-403 treatment groups on day 1. This pattern was again apparent during steady state on day 7 (data not shown).
The interpretation of the ECGs taken before the study began and on day 8 showed that all recordings were within normal limits, with one exception. One woman in the 0.02 mg CQP 201-403 treatment group showed a disturbed repolarisation of the left ventricular wall, a borderline anomaly which was present at baseline and on day 8.

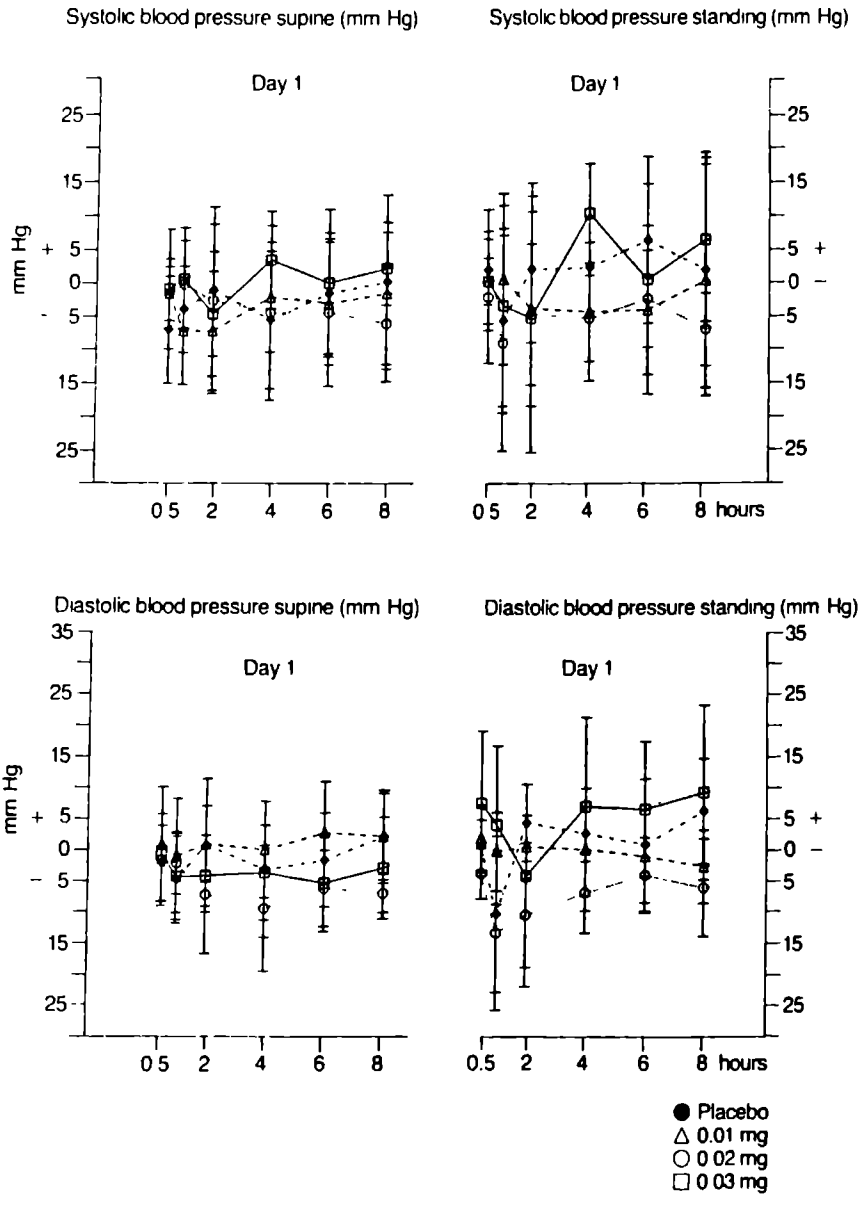

Figure 4. Changes from baseline of systolic and diastolic blood pressure on day one. The data shown are mean values and 95% confidence limits of the three CQP 201-403 groups and the placebo group.

Laboratory safety parameters

In isolated instances, some values appeared outside the normal range for the laboratory. However, for neither urinary nor hematology or blood chemistry measures could any value change be attributed to an action of CQP 201-403.

Adverse reactions

A summary of all adverse reactions is given in table 1, classified according to body system. The adverse reactions, typical of those observed following other dopaminomimetic drugs, were reported most often in the two highest drug dose groups. These reactions, predominantly consisting of dizziness and feeling of faintness, were most often recorded on day 1 between two and four hours after drug intake and were relieved by lying down. Although in some women adverse reactions reappeared on subsequent study days, their number and intensity diminished throughout the week, and in no case was study discontinuation necessary.

Table 1. Number of patients with commonly reported adverse reactions during 8-day observation

Adverse reaction per body system	Treatment			
	0.01 mg (n=6)	0.02 mg (n=6)	0.03 mg (n=6)	placebo (n=6)
Central nervous system				
Dizziness, weakness, faintness	1	6	3	3
Headache	-	4	-	-
Gastrointestinal				
Nausea (vomiting)	1 (-)	3 (-)	2 (-)	-
Respiratory				
Nasal stuffiness	-	-	2	-

Other hormonal parameters

Figure 5 summarizes the changes from baseline (day 1, hour 0) on the serum concentrations of FSH, LH and TSH measured throughout day 1 and day 7. No alterations which could have been attributable to the intake of CQP 201-403 occurred in any of these hormones. Figure 6 shows the changes from baseline (day 1, hour 0) of cortisol; all groups show the expected daytime decrease of this hormone. Growth hormone values are presented in table 2. The isolated spikes occur equally in each group, including the placebo, and all other values are in the normal range.

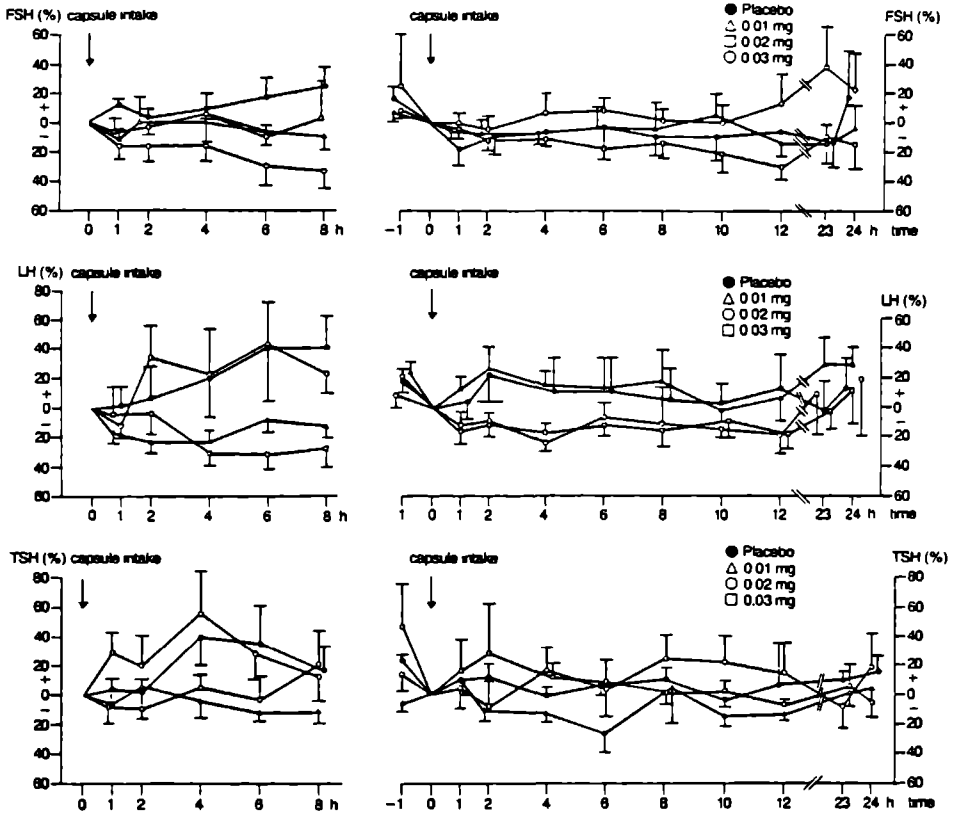

Figure 5. Percentage changes in FSH, LH and TSH from baseline (left-hand panel: day 1, hour 0; right-hand panel: day 7, hour 0) Results are expressed as mean ±SEM.

Table 2. Growth hormone values ≤10 mU/l and incidental spikes (>10 mU/l) in the placebo group and the three CQP 201-403 treated groups on day 1 (acute state) and day 7 (steady state).

state	Group 0.01 mg		Group 0.02 mg		Group 0.03 mg		Placebo	
	acute	steady	acute	steady	acute	steady	acute	steady
Normal range (≤10 mU/l)	35	64	33	65	34	62	34	65
Incidental spikes (>10 mU/l)	1	1	3	1	1	2	2	1
Total number of samples	36	65	36	66	35	64	36	66

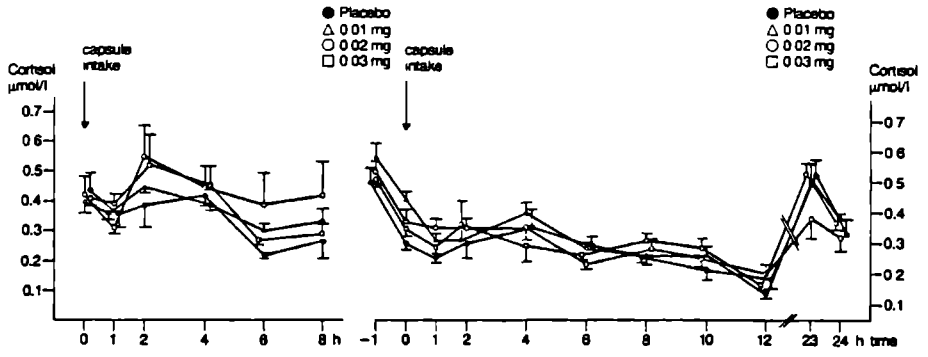

Figure 6. Percentage changes in cortisol from baseline (left-hand panel: day 1, hour 0; right-hand panel: day 7, hour 0). Results are expressed as mean ±SEM.

DISCUSSION

The results of the study reported here allow the conclusion to be made that the new dopamine agonist, CQP 201-403, is a strong and long-acting prolactin supressant compound in patients with hyperprolactinaemia, as previously also demonstrated in healthy volunteers. The marked prolactin-lowering effect, which was apparent on the 1st day of treatment in all dose groups, was sustained at the 0.02 mg and 0.03 mg dose levels during steady state on day 7, when clear indication of a 24-hour action was seen. In these patients serum prolactin suppression reached statistical ($P < 0.05$) and clinical (values to the normal range) significance. This therapeutically relevant effect was accompanied by good drug tolerance, most side-effects being subjective accompaniments of transient postural hypotension. No clinically meaningful alterations in any of the physical, hematological or urine safety tests were seen. On the basis of its facility to suppress prolactin at well tolerated doses, CQP 201-403 would clearly offer an advance in the treatment of hyperprolactinaemia. Bromocriptine, the most extensively used compound available for this indication, is usually given at subclinical doses at the beginning of treatment until the adverse reaction profile improves. Doses must then be given several times daily to sustain suppression. CQP 201-403, on the other hand, with its 24-hour action, can be given once daily, and if taken at bedtime, such side-effects as appeared several hours after morning drug intake in the present study would be avoided. Further studies with CQP 201-403 are therefore warranted to assess its efficacy in hyperprolactinaemic patients treated for longer periods.

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CHAPTER 3

ENDOCRINE EFFECTS OF CV 205-502, A NEW DOPAMINE AGONIST, IN HYPERPROLACTINAEMIC WOMEN

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ABSTRACT

CV 205-502 (CV) is a potent dopaminergic compound which exerts a strong and sustained suppression of prolactin secretion in healthy volunteers

In a prospective double-blind, randomized placebo-controlled trial, 12 hyperprolactinaemic women (> 2000 mU/l), were divided into two groups of 6 women each, treated for 4 weeks Combined pituitary challenge tests (GnRH, TRH, CRH and GHRH) were performed before and after treatment The 6 CV 205-502-treated women (0 05 mg daily) showed approximately a 64% decrease of their initial prolactin serum concentrations after 4 weeks of capsule intake Placebo-treated women showed no change in their prolactin serum level After TRH administration, a blunted prolactin response was present in all women before treatment After CV treatment a trend towards normalization of the prolactin response to TRH was seen, whereas the response pattern in the placebo group remained unaltered

The responses of GH, TSH, LH, and ACTH to their releasing hormones and cortisol showed no significant changes after administration FSH, however, showed a significant decrease in response to LHRH, which could be explained by an increase in estradiol (E_2) as ovarian function normalized in CV 205-502-treated women

In conclusion, CV 205-502 shows strong dopamine agonistic properties in hyperprolactinaemic women treated with 0 05 mg CV daily The profile of this new quinoline compound, as judged from the pituitary challenge tests, does not differ from that of dopamine agonists of the ergoline type

INTRODUCTION

Ergot alkaloids and their synthetic derivatives are prescribed in a variety of diseases. In treating hyperprolactinaemia, acromegaly and Parkinsonism (1), these compounds, like bromocriptine (Parlodel^R), have proved to be very successful. CV 205-502, an octahydrobenzo-[g]-quinoline, is a unique dopamine agonist compound (figure 1), which as well as effecting potent and sustained suppression

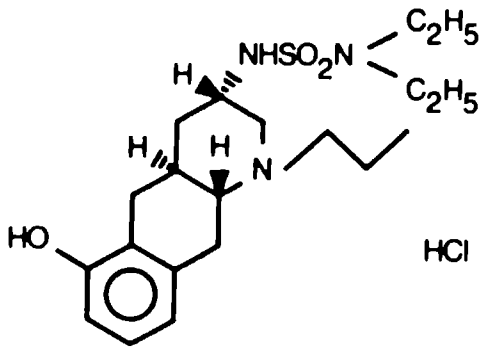

Figure 1. CV 205-502: octahydrobenzo[g]quinoline

of prolactin secretion, is well tolerated, with only a low incidence of adverse reactions in healthy volunteers and in patients (2,3). In order to investigate further the prolactin-lowering efficacy of CV 205-502 in hyperprolactinaemic women and to assess the effect of hypothalamic releasing hormones on the pituitary-thyroid, -adrenal and -gonadal axes and on growth hormone previous to and during steady-state CV 205-502 treatment, pituitary challenge tests were performed.

MATERIALS AND METHODS

Selection of patients

The study was conducted according to the Tokyo amendment of the Declaration of Helsinki (1975). After its design had been approved by the ethical committee of the University Hospital, 12 women who were suffering from hyperprolactinaemia (prolactin persistently above 2000 mU/l) were invited to take part in it. Having received information concerning the trial, all gave their written consent.

Except for their hyperprolactinaemia, they were healthy women aged between 24 and 44 years (mean age 35.1 ± 6.4 (SD) years). The Quetelet index ([weight / height^2]x10^5) was within the normal range for the different age groups (4). Six women were suffering from secondary amenorrhoea. The other 6 had more or less regular cycles before selection. Of these, 3 used bromocriptine which was stopped at least 1 month prior to the study. Only when it had been confirmed that in the absence of bromocriptine their serum prolactin levels had increased to above 2000 mU/l, were these women admitted to the study. The remaining 3 women had more or less regular cycles despite their hyperprolactinaemia. Since in 3 women bromocriptine was stopped rather close to commencement of the study, 6 women in total had menstrual episodes in the period immediately prior to the study. As judged from their menstrual history, 3 were in the follicular phase of the cycle and the remaining 3 premenstrual on the day of the 1st challenge test. None of the women showed signs of a pituitary macroadenoma by routine tomography or CT-scan of the pituitary fossa.

Hormone assays

Serum concentrations of LH, FSH, and TSH were measured with specific double antibody solid-phase based radioimmunoassays developed in our laboratory and described previously (5,6) Prolactin and growth hormone measurements were performed with the Spectria RIAs purchased from Farmos Diagnostica (Turku, Finland) Cortisol was assayed by applying the coated tube RIA available from Baxter Travenol, Clinical Assays Inc (Boston, Massachusetts, USA) E_2 and P were measured with previously described in-house RIAs (7) ACTH was determined by use of an immunoradiometric assay (IRMA) purchased from Eurodiagnostics BV (Apeldoorn, The Netherlands) Assay characteristics are shown in table 1. The assay sensitivities depicted in table 1 are defined by the dose reading at zero-binding minus 2 x the standard error (SE) in the case of RIA, whereas the IRMA applied the dose reading at zero-binding plus 2 x SE Assay precision was calculated from means of duplicate measurements of serum pools (8), and is expressed in percent coefficient of variation (CV) of both within (CVw) and between (CVb) assay variability

Table 1 Standard dose range, sensitivity and precision of the hormone assays

Hormone	Unitage	Standard dose range	Sensitivity	Precision		n
				$\%CV_w$	$\%CV_b$	
LH	IU/l	4 0 250	1 5	8 3	12 5	99
FSH	IU/l	1 6-100	0 35	8 1	12 1	62
TSH	mIU/l	1 0 65	0 70	7 0	8 9	48
PRL	mIU/l	50 5000	30	5 6	8 1	57
GH	mIU/l	1 0 100	0 20	4 1	8 8	30
Cor	nmol/l	30 1700	10	3 2	6 3	92
ACTH	ng/l	20-1000	8 0	3 2	7 0	12
E2	fmol/tube	10 1500	5 0	4 3	7 9	78
P	fmol/tube	50 3200	25	4 1	9 1	36

The specificity of both RIA and IRMA in terms of percent cross reactivities was tested by adding various amounts of relevant peptide or steroid hormones to the different assays and is calculated (9) In the case of Prl, LH, FSH and TSH the cross reactivity of all peptide hormones tested was negligible, except for hCG (human Chorionic Gonadotrophin) which showed a significant cross-reaction of 100% in the LH RIA The cortisol RIA gave a substantial cross-reaction only with prednisolone (73%) and 6-methylprednisolone (18%), whereas the hGH (human Growth Hormone) assay revealed 100% cross-reactivity with hPL (human Placental Lactogen) In the ACTH IRMA the ACTH fragments 1-24, 1-32, and 18-39 did not interfere The P RIA showed some cross-reactivity with 11-deoxycorticosterone (3 8%), whereas E_2 cross-reacted only with E_1 for 1 0% All other steroids tested for both P and E_2 assays showed cross reactions of less than 1%

Statistical procedure

The results of the hormone measurements prior to therapy (6 women in each group) were compared with those obtained during treatment either with CV 205-502 (6 women) or placebo (6 women) to see whether significant changes had taken place. Secondly the results obtained during CV 205-502 treatment were compared with those found for women taking placebo. For both purposes the unpaired and paired Student t tests were used and a $p < 0.05$ was considered as a significant change. To compare the value of a given hormone at time 0 with the peak value, the Wilcoxon signed rank test was used. For the sake of presentation the data of each hormone within the different groups are shown as mean $\pm$ 1 x SEM either in graph or table form.

Study design

The study was performed double-blind and placebo-controlled. The 12 patients were randomized and treated in 2 groups of 6 patients each. CV 205-502 (0.05 mg) or a placebo was given once daily in capsules of identical appearance. Before treatment was started, a combined anterior pituitary function test was performed. The 4 hypothalamic releasing hormones were given intravenously to establish response patterns while the women were hyperprolactinaemic. One month later the challenge tests were repeated to obtain the response patterns while the patients were under CV 205-502 or placebo treatment.
The following releasing hormones were administered in a fixed sequence GnRH (Gonadotropin hormone-Releasing Hormone, Ayerst lab., New York), 100 μg dissolved in 5 ml; TRH (Thyrotropin-Releasing Hormone, Roche Ltd, Holland), 200 μg dissolved in 2 ml; CRH (rat Corticotropin-Releasing Hormone, Bachem AG, Switzerland), 100 ug dissolved in 1 ml; GHRH (Growth Hormone-Releasing Hormone, factor 1-4, Bachem Ltd, Torrance California, USA), 100 μg dissolved in 1 ml.
All challenge tests started at 9.00 hours after an overnight fast and the patients remained in supine position during the first 90 minutes of the test. The releasing hormones (total volume 9 cc) were injected slowly intravenously within a total period of 3 minutes. Before injection 2 blood samples were taken, at -15 and 0 minutes (baseline). Thereafter samples were taken at frequent intervals for 3 hours: 5, 10, 20, 30, 60, 120 and 180 minutes, after the commencement of the injection. They were placed immediately on crushed ice and remained at 4°C until centrifugation had taken place. All serum samples were frozen and stored at -20°C until assayed. For a particular hormone, all samples from one patient were measured within the same assay run. In all samples Prolactin (Prl), FSH (Follicle Stimulating Hormone), LH (Luteinizing Hormone), TSH (Thyroid Stimulating Hormone), ACTH (Adrenal Corticotropic Hormone), GH (Growth Hormone) and cortisol were measured. Estradiol-17β (OE_2) and progesterone (P) were determined only in the baseline samples in the pooled -15 and 0 minute samples.

The next day all women started to take either CV 205-502 (0.05 mg) or the placebo at bedtime and they continued this treatment for 4 weeks.
Possible side-effects were recorded, as were safety measurements (blood chemistry, hematology, urine analysis and ECG). However, this was not the objective of the study and these data will be reported elsewhere as part of a larger study on efficacy, safety and tolerance of CV 205-502 treatment.
After 4 weeks of capsule intake the challenge tests were repeated in exactly the same manner as described above and the collected serum samples were stored until assayed.

RESULTS

Prolactin (figure 2)

Before the challenge tests all women showed clearly elevated prolactin levels, with a mean of 3500 mU/l (± 566) and 3100 mU/l (±463) in the placebo and CV 205-502 groups, respectively. After TRH administration prolactin showed rather blunted or nearly absent response patterns, with small increases and peak levels at 30 minutes, followed by a slow decrease back to baseline. After 4 weeks of drug intake the placebo group showed identical basal prolactin levels and the response to TRH was also unaltered. However, the women treated with CV 205-502 had a significant decrease in basal prolactin, to a mean serum prolactin level of 1266 mU/l (± 335.1 mU/l, $p \leqslant 0.05$). After the TRH administration prolactin increased to a maximum of 2461 mU/l at 30 minutes ($p \leqslant 0.01$ as compared to time 0). This was followed by a gradual decrease back to baseline. The response curve in patients taking CV 205-502 is significantly different both from the curves seen previous to drug intake from those in patients having placebo treatment when the areas under the curve are compared ($p \leqslant 0.02$).

Pituitary gonadal axis

One woman in the group treated with CV 205-502 appeared to have a spontaneous ovulation very close to the basal challenge test (LH 49 IU/l and E_2 910 pmol/l) and has therefore not been included in the presentation of the FSH and LH data. Another woman in the same group was in the luteal phase of the cycle (progesterone 51 nmol/l), whereas all other women in both groups had progesterone levels below 6.3 nmol/l and estradiol levels below 295 pmol/l, indicative of anovulation. After 4 weeks of treatment 3 of the of 6 women in the CV 205-502 group were in the luteal phase (progesterone 23, 39 and 83 nmol/l, respectively), whereas none of the 6 in the placebo group had showed progesterone levels above 4.8 nmol/l and all estradiol levels were below 200 pmol/l. Thus anovulation persisted during placebo treatment, whereas 3 out

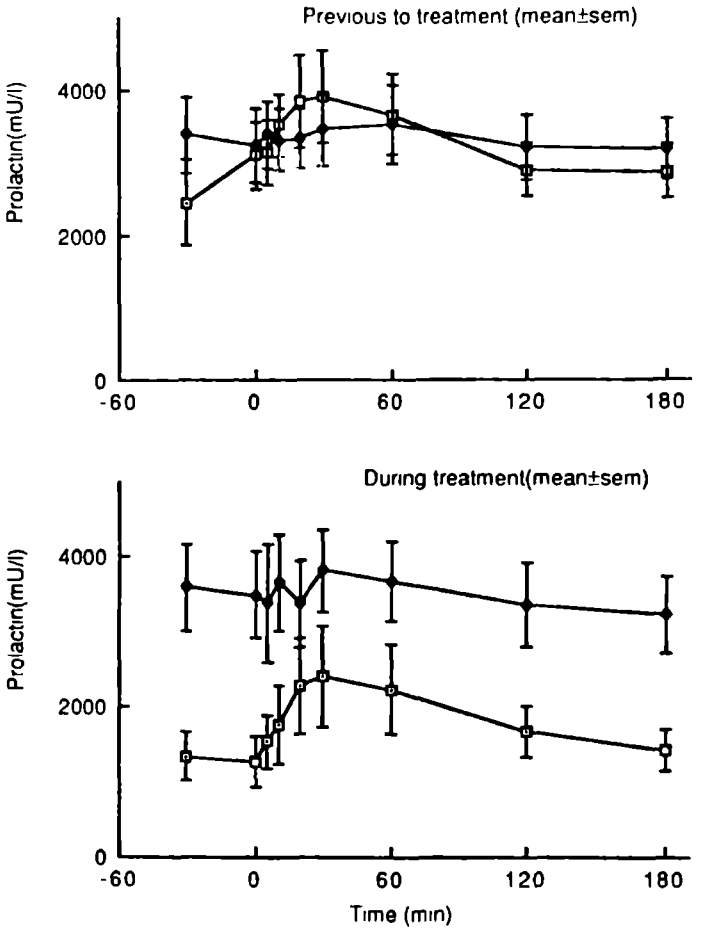

Figure 2. Mean ± SEM serum prolactin levels (mU /L) in 12 hyperprolactinaemic women previous to (upper panel) and after 4 weeks of CV 205-502 versus placebo treatment (lower panel)
Open squares = women treated with CV 205-502 Closed squares = women treated with placebo.

of 6 women in the CV 205-502 treated group had ovulated. The FSH and LH responses are shown in figure 3. With regard to FSH, there was a marked difference between the women treated with CV 205-502 and those treated with placebo, especially during treatment. The LH responses in the basal experiments were nearly identical, as were the responses during treatment. The mean maximum LH response during treatment with CV 205-502 seems lower if compared to the basal experiment, but this difference is not statistically significant.

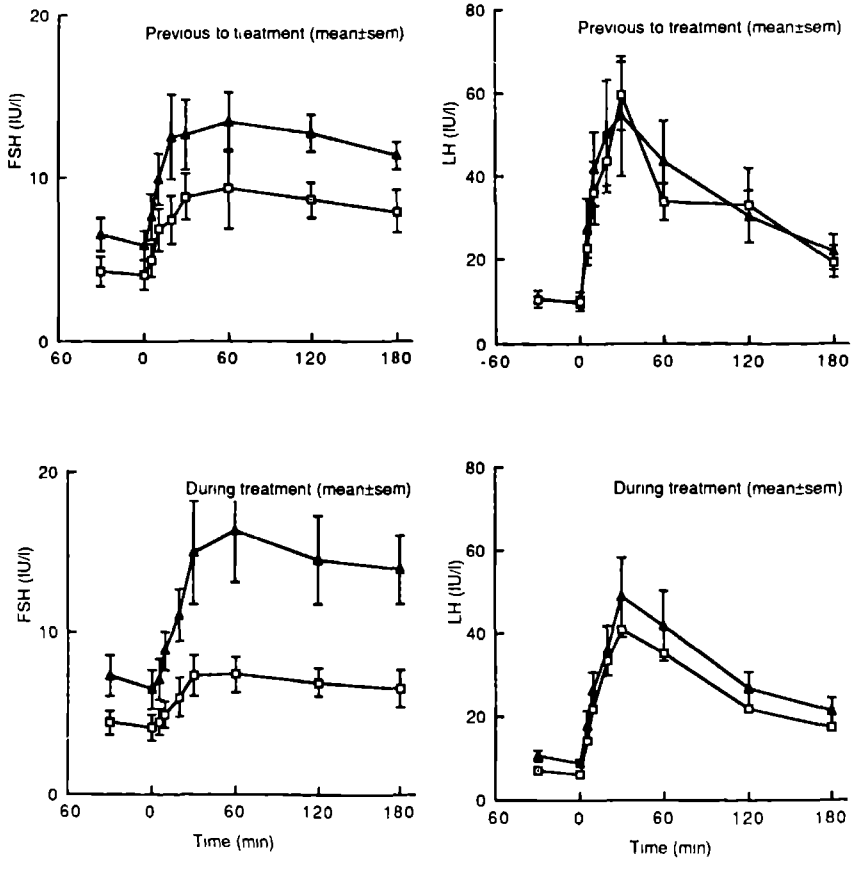

Figure 3 Mean ± SEM serum FSH (U/L, left side) and LH (U/L, right side) in 12 hyperprolactinaemic women Previous to (upper panel) and after 4 weeks of CV 205-502 versus placebo treatment (lower panel)
Open squares = women treated with CV 205-502 Closed squares = women treated with placebo

Growth hormone (figure 4)

Basal growth hormone levels were normal in both groups (t= 0:5.4 ± 2.8 versus 2.4 ± 1.3 mU/l), (p = 0.4). After GHRH administration GH increased rapidly in both groups to a maximum of 30.0 versus 29.6 mU/l at 30 minutes, then decreased thereafter to basal values at 180 minutes. During treatment women receiving placebo capsules showed the same response pattern, although the mean peak value at 30 minutes was lower (23.5±8.3 mU/l). This difference is not statistically significant. However, women treated with CV 205-502 showed a more rapid response to GHRH, with a mean higher maximum level at 30 minutes (36.7±8.7 mU/l). This difference is also not significant (p = 0.3). At 180 minutes GH was back within the normal range in both groups.

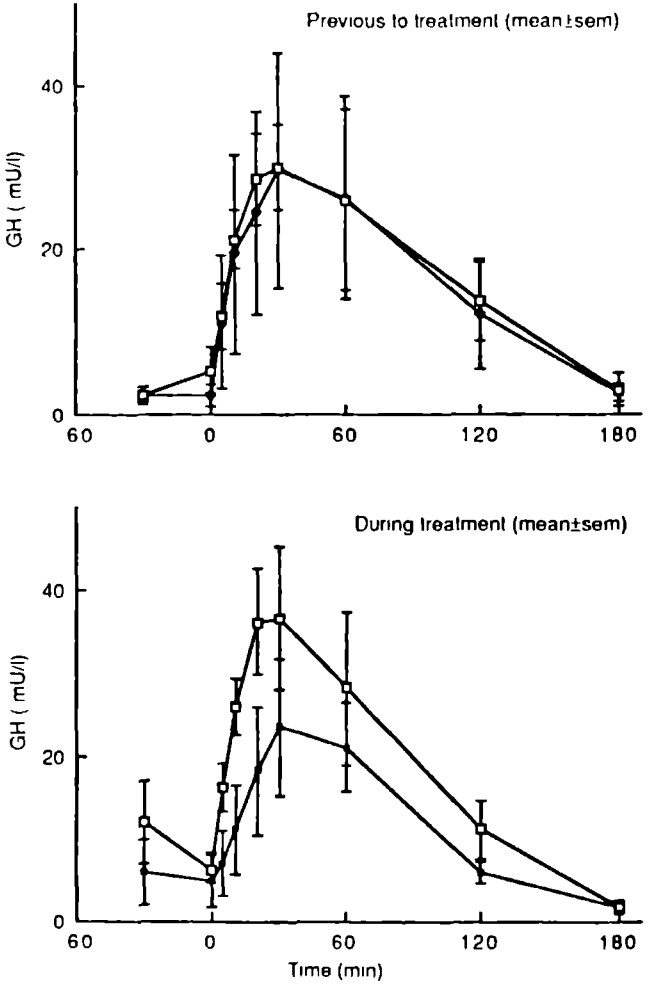

Figure 4 Mean ± SEM serum growth hormone levels (mU/L) in 12 hyperprolactinaemic women previous to (upper panel) and after 4 weeks of CV 205-502 versus placebo treatment (lower panel) Open squares = women treated with CV 205-502 Closed squares = women treated with placebo

Thyroid stimulating hormone

The TSH responses to TRH are shown in figure 5. The response patterns before and during CV 205-502 or placebo treatment are practically identical, indicating no effect of CV 205-502 on the pituitary capacity to release TSH

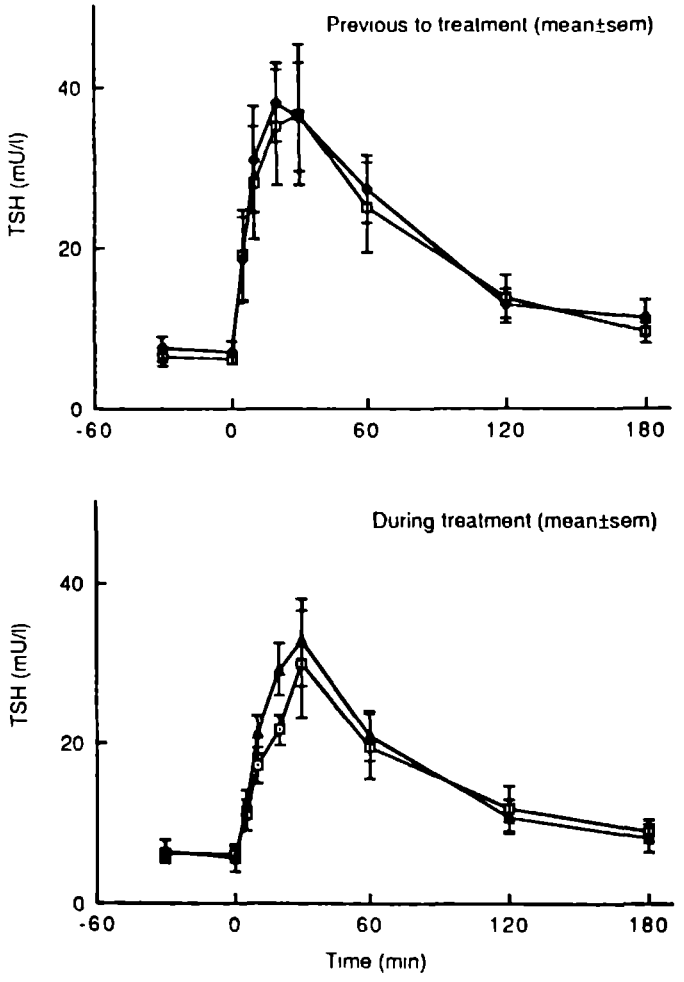

Figure 5. Mean ± SEM serum TSH (mU/L) in 12 hyperprolactinaemic women previous to (upper panel) and after 4 weeks of CV 205-502 versus placebo treatment (lower panel).
Open squares = women treated with CV 205-502 Closed squares = women treated with placebo.

Pituitary-adrenal axis

Figures 6 and 7 show the mean values (±SEM) of ACTH and cortisol in both groups during the basal and treatment experiments. The wide scatter of ACTH values in the CV 205-502 group previous to treatment is striking, but the groups are not significantly different at any time point. During capsule intake the responses in the 2 groups were practically identical, indicating no effect of CV 205-502 on the pituitary capacity to release ACTH in response to CRH. During

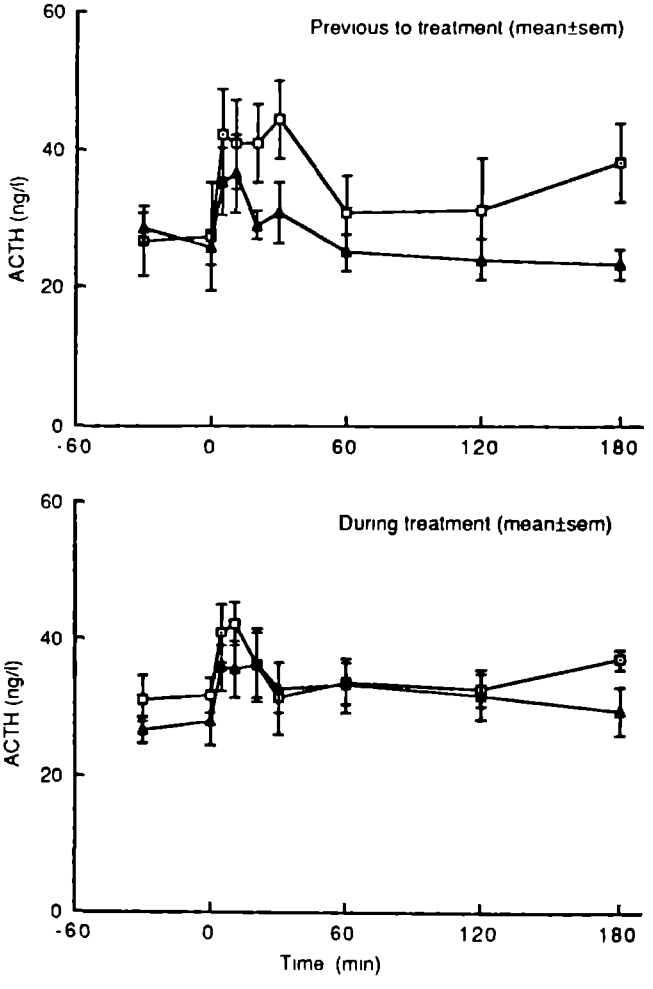

Figure 6. Mean ± SEM serum ACTH (ng/L) in 12 hyperprolactinaemic women previous to (upper panel) and after 4 weeks of CV 205-502 versus placebo treatment (lower panel).
Open squares = women treated with CV 205-502. Closed squares = women treated with placebo.

both the basal experiment and placebo or CV 205-502 treatment there were no changes in the response curves of cortisol, which remained nearly identical, indicating no effect of CV 205-502 on cortisol. The tendency to lower cortisol values at the end of the experiments (t=180 minutes versus t=0) is easily explained by the known decrease of cortisol during the day.

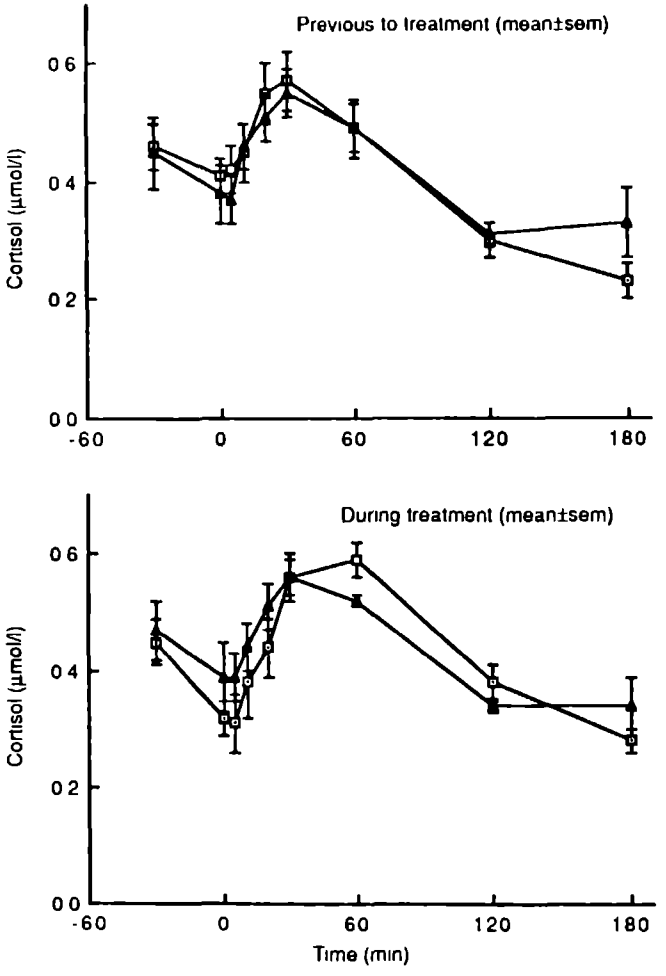

Figure 7 Mean ± SEM serum cortisol (umol/L) in 12 hyperprolactinaemic women previous to (upper panel) and after 4 weeks of CV 205-502 versus placebo treatment (lower panel).
Open squares = women treated with CV 205-502 Closed squares = women treated with placebo.

DISCUSSION

The novel dopamine agonist CV 205-502 (octahydrobenzo[g]quinoline) has previously been shown to exert an excellent prolactin lowering effect with good tolerance in normoprolactinaemic volunteers and in hyperprolactinaemic patients (2,3). This is also true for dopamine agonists of the ergoline type, such as bromocriptine, although such compounds are poorly tolerated by normoprolactinaemic and even some hyperprolactinaemic subjects (1). Futhermore, CV 205-

502 has an extended biological half-life as compared to bromocriptine; consequently, once-daily administration is sufficient to ensure effective prolactin suppression over the next 24-hour period (2). In this study the strong prolactin-lowering effect was again demonstrated in hyperprolactinaemic women, as the six women receiving CV 205-502 showed a significant decrease in serum prolactin, from 3100 mU/l (±463 mU/l) to 1266 mU/l (±335 mU/l), after 4 weeks' intake of 0.05 mg daily, in contrast to the placebo treated group. Since dose-finding studies with this compound in hyperprolactinaemic women have not yet been reported, it is no surprise that not all the women treated with it had normalized their serum prolactin levels by 4 weeks, as the initial dose might not have been adequate. As the drug has very few side-effects and is very well tolerated, a higher starting dose seems justified.

The main reason for performing this study was to evaluate the effects of combined challenge tests with hypothalamic releasing hormones in hyperprolactinaemic women both while receiving no treatment and while being treated with CV 205-502 or placebo, to look into the effects of this new dopamine agonistic compound on pituitary function. As in many previous studies (10), we also combined several releasing hormones. This is justified by the fact that no synergism or inhibition in the hormonal response to these releasing hormones has been shown whether they are presented combined or when each releasing hormone has been given separately (11). However, some reports have suggested that in combined challenge tests the TSH response to TRH might be enhanced (12). Even if this is so, it does not influence the validity of the present study, as, if a difference in the TSH response to TRH had appeared during CV 205-502 treatment, it could have been attributed only to either the normalization of prolactin or a direct effect of the drug, since results previous to and during drug treatment and those of the placebo group were compared. It can therefore be concluded that administration of CV 205-502 does not influence the pituitary capacity to release TSH in response to TRH. This is in agreement with previous studies where TSH was measured in hyperprolactinaemic women before and during bromocriptine treatment (12,13).

The results of the present study confirm previous findings that CV 205-502 shows strong prolactin suppressant properties in hyperprolactinaemic women (3), such as those seen in normoprolactinaemic male volunteers (2) and also confirm the finding that hyperprolactinaemic women show a blunted or even absent prolactin response to TRH (14). In healthy normoprolactinaemic women, serum prolactin also increases by 4-5 times in response to a challenge by TRH (15). After administration of CV 205-502 to the male volunteers this prolactin response appeared blunted and the explanation was thought to be the blocking effect of the compound at the level of the lactotrophs (16). This differs from the findings in the present study, which clearly show a trend towards normalization of the prolactin response to TRH in women taking CV 205-502 and furthermore agree with findings in postpartum women treated with bromocriptine for the purpose of inhibition of lactation. In the latter women a trend towards nor-

malization is seen when they are given TRH within 3 weeks of delivery, during the course of bromocriptine treatment (17) In vitro studies by Pasteels et al (18) also showed that although spontaneous prolactin release by normal pituitary tissue is inhibited when dopamine agonists are added to the culture medium, addition of TRH gives rise to an increased release of prolactin It is therefore suggested that although dopamine agonists block the release of the hormone at the level of the lactotrophs, these cells remain capable of responding to TRH for at least 3-4 weeks Since the lactotroph response is the inability to release prolactin, and perhaps also the synthesis of new hormone, it may be that after a longer period of treatment the cells become unresponsive to TRH since they have become completely depleted of prolactin

Infusion of dopamine inhibits the release of growth hormone release inhibiting factor (SRIF) (19) From a theoretical point of view one could assume that this would give rise to an exaggerated GH response to GHRH This is also demonstrated in the present study, although the increase in response is rather small It is also known that dopamine itself inhibits the GH release at the pituitary level (20) The observed ch ges in the GH response to GHRH in the present study might therefore be expl. ied by competition between these two mechanisms It should be stressed that although these changes do occur, basal growth hormone levels remained within normal limits in women treated with CV 205-502 If treatment is continued beyond several weeks, the GH response to GHRH also normalizes (21)

Numerous studies have shown that as serum prolactin normalizes in hyperprolactinaemic women treated with dopamine agonists, so does the function of the ovary with restored fertility (22) Although recording ovarian function was not the aim of this study, a trend towards normalization was noted in the six women who were given CV 205-502 Of these, 3 had ovulated within 4 weeks of treatment, as compared to none in the placebo group Indeed an extended study in 41 hyperprolactinaemic women has shown that within 3 months of initiation of CV 205-502 treatment 19 out of 25 previously amenorrhoeic women re-initiated their cycles (see chapter 4) The exaggerated FSH response to GnRH prior to treatment in all women and persisting in placebo-treated women is well in agreement with previous findings in hyperprolactinaemic women (23) Such a response pattern is also seen in amenorrhoeic-normoprolactinaemic women with impaired pulsatile release of GnRH (24) and suggests that their failure to maintain normal ovulatory cycles while being hyperprolactinaemic is due to a defect at the hypothalamic level Surgical removal of prolactin-producing pituitary tumors also restores ovarian function and this suggests that the hypogonadism observed in hyperprolactinaemic women is due to a short-loop feedback of prolactin itself at the level of the hypothalamus The hypothalamic-pituitary-adrenal axis was not influenced by the intake of CV 205-502 This is in agreement with previous reports showing no change in this axis in healthy volunteers treated with CV 205-502 (16) and in hyperprolactinaemic women with or without other dopamine agonist therapy (25)

It is concluded that the profile of CV 205-502 as judged from these challenge studies is not different from that of other dopamine agonistic drugs such as bromocriptine, despite the non-ergot structure of the drug Since the drug is well tolerated and once daily administration at bedtime is sufficient to maintain adequate prolactin suppression over a 24-hour period (26) it is suggested that this compound may become a welcome alternative to the dopamine agonistic drugs currently available

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CHAPTER 4

THE EFFECTIVENESS, SAFETY AND TOLERABILITY OF CV 205-502 IN HYPERPROLACTINAEMIC WOMEN: A 12-month study

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ABSTRACT

Forty-one hyperprolactinaemic women (prolactin (PRL) > 2000 mU/L) were treated between 12 weeks and 52 weeks with the new nonergot, long-acting dopamine agonist octahydrobenzo[g]quinoline (CV 205-502) The treatment resulted in normalization of PRL secretion in 71% of the women at a once-daily dose of ≤0 100 mg All women responded with a significant decrease in serum PRL Menstrual function normalized in all women except 1, whereas galactorrhoea disappeared in all but 2 patients During the observation period, four pregnancies were recorded with an additional three in the immediate post treatment period Until now four healthy children have been born Regarding tolerability, women with fair or poor responses to bromocriptine (Parlodel®) in the past, tolerated CV 205-502 better Two women with no PRL decrease while on Parlodel®, responded with a decrease while on CV 205-502 All safety parameters remained normal while on treatment, and no significant changes were observed in blood pressure (supine and standing), pulse rate, or electrocardiogram (ECG) recordings CV 205-502 therefore seems to be a valuable new compound in the management of patients with hyperprolactinaemia

INTRODUCTION

Dopamine agonists have become the treatment of choice in hyperprolactinaemia and the inhibition of puerperal lactation and are also widely used in the indications of acromegaly and Parkinsonism (1). Bromocriptine (Parlodel^{R}; Sandoz Ltd., Basle, Switzerland) is very effective in the suppression of serum prolactin (PRL), but may in some patients give rise to side effects like nausea, gastric upset, peripheral vasospasm, and orthostatic hypotension, especially at initiation of therapy. Due to its relatively short duration of action, it is recommended to take the drug two or more times daily to ensure normoprolactinaemia (2). CV 205-502 (octahydrobenzo[g]quinoline) is a new PRL-suppressant drug (3). It

is the first nonergot dopamine agonist designed as a specific D_2 receptor agonist and should, therefore, have a profile with less dopaminergic side effects because these depend more on D_1 receptors (4). Both in animal studies and in normoprolactinaemic human volunteers and hyperprolactinaemic patients (5-8), CV 205-502 has shown a strong PRL-lowering effect at once-daily administration (5). In dosages giving PRL suppression of 58% to 70% the drug was well tolerated, although in higher dosages, side effects like sleepiness and headache have occurred (6-8). No clinically relevant changes were observed in laboratory blood and urine tests, electrocardiograms (ECG), or physical examinations. Due to this promising profile of CV 205-502, it was decided to test the PRL lowering capacity in hyperprolactinaemic women, and the two following objectives were formulated a: to ascertain the dosage at which CV 205-502 exerts a clinically relevant PRL suppressant effect in hyperprolactinaemic patients, and b: to assess at regular intervals throughout a 12-month period the safety and tolerability of the drug.

MATERIALS AND METHODS

The study was conducted according to the Tokyo amendment of the Declaration of Helsinki. After approval by the hospital ethical committee, all patients gave their written, informed consent to participate. Forty-one women suffering from hyperprolactinaemia, with serum PRL levels persistently >2000 mU/l (normal, < 800 mU/l, 36 mU/L = 1 ng/ml) on at least two occasions during the month preceding the study, agreed to participate. Except for their hyperprolactinaemia, they were all healthy women between 18 and 49 years of age. By routine radiography or computerized tomographic (CT) scanning of the pituitary fossa, none of them had signs of a macroadenoma. All women agreed to participate for a 12-week period unless side effects required discontinuation of the drug. Those who wanted to continue were allowed to do so for a treatment period of 52 weeks. Of these 41 women, 5 had spontaneous menstrual periods despite their hyperprolactinaemia. Twenty-five women had secondary amenorrhoea (> 6 months) and 11 oligomenorrhoea (6 weeks to 6 months). Twenty-five of the 41 women were suffering from galactorrhea. Twenty women were involuntarily infertile and 11 of them wanted to become pregnant during the study once their cycle had normalized and at least 3 consecutive menses had been monitored. During the first 4 weeks the study was conducted as double-blind, and the participating women were randomly assigned to receive either placebo or CV 205-502 at a dose of 0.05 mg once daily. After 4 weeks the code was broken, and the placebo treated patients were also started on 0.05 mg CV 205-502. In the drug treated group, the daily dose of CV 205-502 was increased after 4 weeks by 0.025 mg for the next 4 weeks if the PRL suppressant effect of CV 205-502 was judged insufficient (a PRL decrease of < 50% as compared with the previous value). If PRL again showed inadequate suppression, a further increase of the dosage was advised in monthly steps of 0.025 mg to a maximum

of 0.150 mg. In case of poor tolerance the dosage could also be decreased by 0.025 mg/d. The women who started on placebo followed the same sequence of possible drug increase/decrease, except that they started intake of CV 205-502 four weeks later.

The medication sets were supplied according to a computer-generated randomization list providing for code number assignment by blocks of four to ensure that approximately one-half of the patients received placebo treatment for the first 4 weeks. The capsules of active drug and placebo were of identical appearance and were both supplied in blister packets, each packet containing 28 capsules. All capsules were taken once daily at bedtime with a little snack throughout the study.

Before therapy a physical examination and extensive blood and urine analyses were all normal. All pretreatment ECG recordings were also clinically normal. All these items were repeated throughout the study at 4-week intervals. PRL, body weight, blood pressure and pulse rate (supine and standing) were also recorded before the study, at 2-week intervals during the first 12 weeks of the study and thereafter every 4 weeks. At each visit the women were examined for the presence of galactorrhoea and questioned regarding the regularity of the cycle and the occurrence of adverse reactions.

Pretreatment findings in the two groups are shown in table 1. From this table it can be concluded that the randomization was successful. Most of the participating women had been treated with Parlodel® in the past (active drug group 20, placebo group 18). Regarding tolerability, 17 of these women had

Table 1 Anamnestic and descriptive data of patients starting with CV 205-502[a] or placebo[b]

Item	CV group	Placebo group
No of women	21	20
Age (y)	1 6 ± 1 54	32 3 ±1 33
Height (cm)	167 0 ± 1 27	166 1 ± 1 83
Weight (kg)	64 4 ± 1 8	67 6 ± 2 0
Parity		
multiparae	12	11
nulliparae	9	9
Galactorrhoea	12	12
Infertility[c]	10	10
Amenorrhoea[d]	11	14
Oligomenorrhoea[e]	6	5
Previous Parlodel® use	20	18

[a]CV 205-502, octahydrobenzo[g]quinoline

[b]Expressed as mean ± standard error of the mean or No of women (n)

[c]More than 1 y

[d]More than 6 mo

[e]More than 6 wk to < 6 mo

responded favorably to Parlodel®, 12 women showed a fair response, and 9 poor Twenty-eight women showed a good PRL lowering response to Parlodel®, and 8 a fair response, whereas 2 did not respond at all The responses good, fair, and poor were defined as follows good - the tolerated dose led to normalization of serum PRL, fair - the tolerated dose led to >50% decrease in serum PRL, but no normalization was achieved, and poor - the maximal tolerated dose led to <50% decrease in serum PRL

After 12 weeks of treatment, 11 of the 41 women discontinued the intake of CV 205-502 for personal reasons, and none of them stopped due to intolerability of the drug Therefore, 30 women continued intake of CV 205-502 beyond 12 weeks Of these women, 14 came from the group that started with placebo instead of CV 205-502 for the first 4 weeks

PRL was measured by use of the Spectria radioimmunoassay (RIA), purchased from Farmos Diagnostica (Turku, Finland) The sensitivity of this assay is 30 mU/l, with an intra-assay and interassaycoefficient of variation of 5 6% and 8 1%, respectively The upper limit of normal in menstruating women is 800 mU/L All other laboratory measurements (blood hematology, chemistry and urine) were performed applying specific and sensitive standard laboratory procedures All results are expressed as geometric mean values ± standard error of the mean (SEM) and Student t test for paired observations was used for calculations of differences between mean values

RESULTS

Prolactin

In table 2 an overview is given of the changes in serum PRL levels in all women during the active treatment phase with CV 205-502 Because at the start of capsule intake 20 women took placebo capsules for 4 weeks, the duration of treatment with active drug in this group is 4 weeks shorter (maximum duration 48 weeks) Mean PRL concentrations decreased from 3526 ± 416 to 784 ± 125 mU/l at 12 weeks in the group started on CV 205-502 and from 3175 ± 378 to 688 ± 144 mU/l in women started on placebo

At this time 5 women discontinued treatment, 3 of whom had normalized their serum PRL in the CV 205-502 starting group At 8 weeks of active treatment 6 women in the placebo starting group discontinued CV 205-502 use, 5 of whom had already normalized their PRL serum concentrations Twenty-four women were treated for 52 weeks, whereas 6 women discontinued treatment between 12 and 52 weeks Of these 6 women, 4 became pregnant with normal PRL levels at the time of conception, and 2 women discontinued treatment for other reasons with normal PRL serum concentrations at the time of discontinuation At 52 weeks, only 3 women had not normalized their serum PRL levels (2100, 1000 and 990 mU/l, respectively) This means that the percentage of women in the group under treatment rather resistant to CV 205-

Table 2 Serum prolactin levels (mU/l) in the CV 205-502 group (CV) and the placebo-started group (Placebo/CV) throughout the study period

	Month							
group CV	0	0.5	1	1.5	2	2.5	3	4
n[a]	21	20	21	21	21	20	21	16
Mean	3526	1209	1317	1047	1033	919	784	855
SEM	416	215	234	179	203	161	125	244
Minimum	990	100	100	100	100	100	100	100
Maximum	9260	3200	4200	3100	4000	2600	2200	4100
% decline	0	66	63	70	71	74	78	76
PLACEBO/CV								
n[a]	20	20	20	20	20	19	19	14
Mean	3175	3070	3130	1043	970	819	688	985
SEM	378	361	391	213	212	165	144	239
Minimum	1300	1200	610	100	100	100	100	100
Maximum	6400	6600	6800	4200	3900	2800	2400	2800
% decline	0	4	2	67	69	74	78	69

	Month							
group CV	5	6	7	8	9	10	11	12
n[a]	15	15	13	11	11	12	13	12
Mean	916	737	786	813	929	523	767	615
SEM	167	123	168	205	208	87	196	156
Minimum	220	190	270	270	280	100	150	230
Maximum	2500	1900	2500	2700	2400	1100	2900	2100
% decline	74	79	78	77	76	85	78	83
PLACEBO/CV								
n[a]	12	13	13	13	7	10	12	11
Mean	921	774	642	558	771	711	596	558
SEM	200	186	120	145	247	199	129	155
Minimum	100	100	100	100	100	100	100	100
Maximum	2400	2100	1500	2000	2100	2000	1700	1900
% decline	71	76	80	82	76	78	81	82

[a]No of women

502 increased (negative selection). In figure 1 mean PRL levels were shown during active treatment with CV 205-502. The inset shows also the mean PRL curve using the last PRL measurement of each woman who stopped active treatment between weeks 8 and 48 or 12 and 52, respectively at each time point thereafter. Table 3 summarizes the (pre)treatment PRL levels in all women in relation to the dose of CV 205-502 that was used at the time of discontinuation

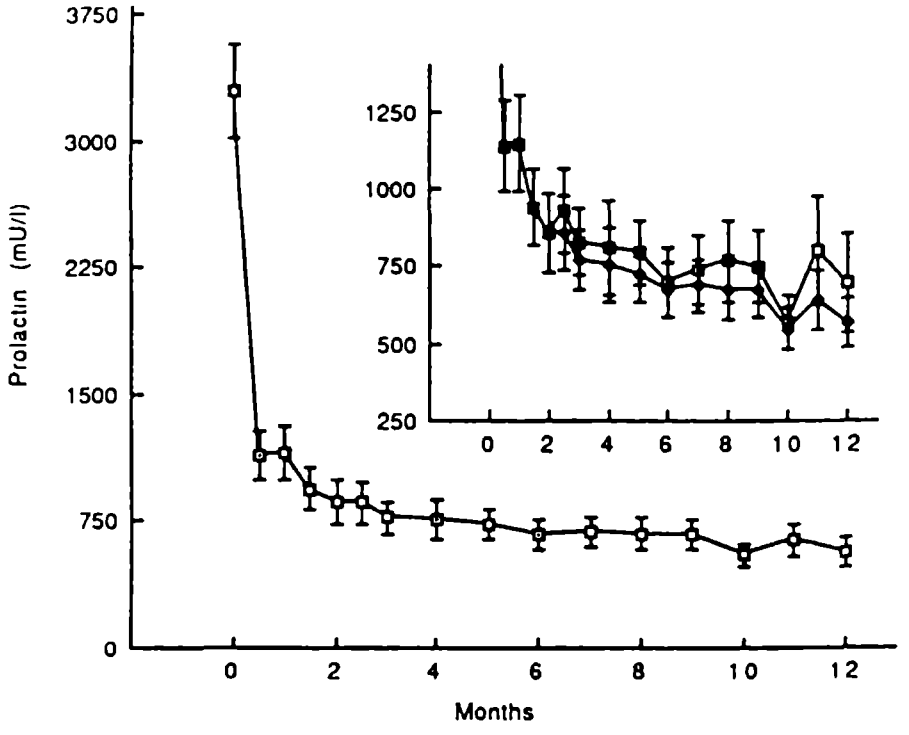

Figure 1 Mean serum prolactin (±SEM) during active treatment with CV 205-502 (open squares) Inset Same data and mean serum prolactin (±SEM) if the last measured serum prolac-tin level in each woman who discontinued treatment before 52 weeks is taken into account at each time period thereafter (closed diamonds)

Table 3 Prolactin concentrations[a] before and at discontinuation of CV 205-502 intake in relation to the dosage of the drug at discontinuation

CV dosage at discontinuation of treatment mg	No of women	Pretreatment prolactin concentration mU/l	Prolactin concentration at discontinuation mU/l	Women with prolactin < 800 mU/l	
				No	Percent
0 05 mg	17	2081 ± 238	256 ± 41 6	17	100
0 075 mg	8	3587 ± 509	505 ± 95 4	6	75
0 100 mg	9	3789 ± 356	885 ± 140 5	6	66
0 125 mg	1	4700	250	1	
0 150 mg	6	5327 ± 947[b]	1255 ± 246 9	1	17

[a]Results are expressed as mean ± standard error of the mean
[b]Less than 0 01 as compared with 0 050 mg

of drug intake or at 52 weeks and also indicates the number of women who had normalized their PRL level (< 800 mU/l) Of 41 women, 71% normalized their serum PRL on a CV 205-502 dose of ⩽ 0 100 mg

Menstrual Cycle

Within 12 weeks of active treatment 19 of the 25 amenorrhoeic women had menstruated at least once, and at the end of treatment only 1 woman was still suffering from amenorrhoea Her serum PRL concentration at the end of treatment was 990 mU/l In the 11 women complaining of oligomenorrhoea, the cycle normalized and became regular within 8 weeks in all of them Pregnancies occurred within the 12-month period in 4 of the 11 infertile women Mechanical contraception was only to be stopped when the cycle had become regular, which explains why the pregnancies occurred between 4 and 11 months of active treatment, i e , in months 4, 6, 10, and 11 Two pregnancies ended in spontaneous abortions, the other two produced healthy children After 52 weeks pregnancies occurred in 3 additional women

Galactorrhoea

Spontaneous milk discharge and discharge by palpation improved significantly or disappeared completely within 12 weeks in 13 of the 24 women with this complaint At the end of the treatment period at 52 weeks, only 2 women still reported mild galactorrhoea The last measured serum PRL levels in these two women were 2100 and 530 mU/L, respectively

Tolerability

During the first 4 weeks, dizziness and tiredness were reported once in both groups Acne was reported as a side effect once in the placebo group Only nausea (6 in the CV 205-502 group and 1 in the placebo group) and headache (7 versus 4) were reported more frequently in the CV 205-502 group at 2 weeks of treatment, but not any longer at 4 weeks Thus, the adverse reactions occurring mostly at the beginning of treatment, were mild or occasionally moderate in intensity and in none of the women led to study discontinuation During the remaining 9 months, the adverse reactions disappeared except for slight nausea which remained in two patients This complaint was not dose related and was noted especially during the night if awake

In the 12 women treated with Parlodel® in the past whose tolerability was judged to be fair, none reported adverse reactions during treatment with CV 205-502 severe enough to demand study discontinuation Also, the 9 patients with poor tolerance of Parlodel® in the past could continue the use of CV 205-502 with

considerably fewer side effects The 2 patients who did not respond at all with a lowering of their serum PRL level while treated with Parlodel® (maximum dose 40 and 15 mg, respectively) showed a significant decrease of prolactin while under treatment with CV 205-502 (PRL decline from 6400 and 5800 to 990 and 2100 mU /l, respectively), on dosages of 0 150 mg

Safety

No clinically significant effects on blood pressure were observed at any of the visits nor did any of the women express complaints indicating orthostatic hypotension Extensive haematological and biochemical parameters in blood and urine, measured normal at baseline, remained so without clinically significant changes that could be attributed to treatment with CV 205-502 Also all physical examinations remained without changes throughout the study In eight women, five in the placebo started group, ECG changes were observed during the study period These changes occurred in both directions (from normal to borderline and vice versa), and in no case was an alteration judged clinically significant Changes were seen as those that may occur when serial ECGs are recorded within the same population over a longer period of time No clinical symptoms or signs of heart problems developed

DISCUSSION

The objectives of this study were to ascertain the dosage at which CV 205-502 exerts a clinically relevant PRL suppressant effect in hyperprolactinaemic patients and also to assess tolerability and safety of this drug The 41 patients who volunteered were all suffering from persistent hyperprolactinaemia with PRL levels $>$ 2000 mU /L From the fact that 71% of them normalized their serum PRL levels with a dose of CV 205-502 of $\leqslant$ 0 100 mg once daily, the effectiveness of this drug is clearly demonstrated

Not all women normalized their PRL levels during this 12-month study This is at least in part explained by the fact that the dosage could only be increased to 0 150 mg /d After the 12-month period, these women have been followed further with a gradual increase in the dose of CV 205-502 to a maximum of 0 500 mg once daily at time of preparing this paper Within this dose range, all women except two have responded with a complete PRL normalization These 2 women have, however, shown significant decrease in their serum PRL concentrations from 6400 and 5800 to 990 and 2100 mU /l respectively The majority of the women had been treated with Parlodel® in the past, of which 21 showed a fair or poor response to this drug It is interesting to note that all of them showed a significant decrease in their serum PRL levels while treated with CV 205-502 Even more promising is the fact that the 8 women with a fair response to Parlodel® in the past all normalized their serum PRL levels

while treated with CV 205-502, whereas the 2 Parlodel® nonresponders also showed significant PRL decrease while treated with CV 205-502. Therefore, this study strongly suggests that CV 205-502 is at least as effective in its serum PRL- lowering capacity as Parlodel® is. However, prospective, double-blind trials have to prove this hypothesis. These studies are at present ongoing.

An important observation during this study was the fact that all women could continue the intake of CV 205-502 for at least 12 months and none of them discontinued due to intolerability. As mentioned in the introduction, CV 205-502 has specifically been designed as a D_2 receptor agonist with low binding to the D_1 receptor (4). The remarkable observation that all women tolerated CV 205-502 very well proves that this approach to drug design is successful. This is further underlined by the fact that women tolerating Parlodel® rather poorly all could continue treatment with CV 205-502 and also told the observers that, in comparison with Parlodel®, in their opinion, the tolerability of CV 205-502 was better. As for the PRL suppressant effect of CV 205-502 the ongoing prospective, double-blind trials have to prove whether CV 205-502 is, indeed, better tolerated than Parlodel®. Although the drug is a specific D_2 receptor agonist, a favorable effect in eliminating side effects may also be due to the longer pharmacological action of the drug (5). Therefore, it is sufficient to administer the drug once daily at bedtime, as side effects are less likely to be noticed during sleep.

Several studies have shown in the past that as PRL normalizes while on dopamine agonist treatment, galactorrhoea improves or disappears and fertility is restored (9-14). Although this was not the aim of this study, the observations of pregnancies while on CV 205-502 and the disappearance of galactorrhoea, indeed, indicate that CV 205-502 in this respect is not different from other dopamine agonists. Until now four children have been born to women in whom conception took place while on CV 205-502 treatment. All children have been healthy. No special caution is necessary in pregnancy concerning the use of CV 205-502. Animal data have shown no harmful effects of the drug to offspring (15), and all clinical studies published so far (6-8), as well as the data from this study, indicate that CV 205-502 is safe. The extensive tests of urine, blood and biochemical parameters did not reveal any significant change from normal. Also, while on treatment, physical examinations, blood pressure, and pulse rate remained within normal range. Of special interest is the fact that no significant changes were observed indicating orthostatic hypotension, although we took great care to measure both the blood pressure and pulse rate exactly after 3 minutes' standing. Other dopamine agonistic drugs like Parlodel® indeed give rise to a significant change in blood pressure while changing posture (1). From a clinical point of view, all ECG recordings remained normal while on treatment, although from time to time some changes were seen. However, no complaints or findings indicated changes in cardiac function while on treatment.

We therefore conclude that CV 205-502 shows very promising PRL lowering effects in hyperprolactinaemic women. It is also a well-tolerated drug, and we

suggest that the basic dose should be 0 075 mg once daily at bedtime instead of 0 050 mg

Although >70% of all women with PRL-related gynaecological disorders will normalize their serum PRL level on 0 100 mg once daily, our data also indicate that the higher the serum PRL level at initiation of therapy, the higher the dosage of CV 205-502 necessary to normalize prolactin We therefore also suggest that in women with very high prolactin levels, CV 205-502 should be increased rather rapidly stepwise from 0 075 mg a day to 0 150 mg/d, etc The drug appears safe, well tolerated and while PRL normalizes, galactorrhoea disappears and fertility restores Further prospective, randomized, and double-blind trials have to prove the superiority of CV 205-502 as compared with Parlodel® and the safety of offspring resulting from treatment

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CHAPTER 5

CV 205-502, A NEW DOPAMINE AGONIST, VERSUS BROMOCRIPTINE IN THE TREATMENT OF HYPERPROLACTINAEMIA

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ABSTRACT

Forty seven hyperprolactinaemic patients with serum prolactin (PRL) concentrations persistently above 1500 mU/l were treated with the new dopamine agonist CV 205 502 or bromocriptine in a prospective, randomized and double-blind fashion during a 24-week period Two women had to be excluded because of poor compliance in the first month Therefore 45 patients remained for evaluation 81% of the patients in the CV 205 502 group and 70% of the patients in the bromocriptine group normalized their prolactin levels within the study period with a treatment dose as permitted in this protocol In general serum prolactin normalized within 8 to 12 weeks of treatment There were no differences between the two tested drugs regarding restoration of the menstrual cycle or disappearance of galactorrhoea Both drugs gave rise to adverse reactions, especially during the initiation of therapy However, the adverse reactions reported during CV 205-502 treatment were less severe and persistent than those attributed to bromocriptine Patient acceptance of the new drug with regard to tolerability was judged by 90% of the women in that treatment group as very good or good, while 75% of those treated with bromocriptine evaluated its tolerability as very good or good

We conclude that CV 205-502 is highly effective in the treatment of hyperprolactinaemia with concomitant restoration of gonadal function and prevention of galactorrhoea The tolerability of the drug seems better than of bromocriptine and therefore this drug is of value in the treatment of hyperprolactinaemic patients

INTRODUCTION

The ergot alkaloid derivative bromocriptine has become the standard dopamine agonist for the treatment of hyperprolactinaemia (1-4). Although in general well tolerated, its use has been hampered in some individuals by its adverse reactions (5-6). This is especially so in women with mild hyperprolactinaemia. A new dopamine agonist with a better side effect and adverse reaction profile could therefore be of value. CV 205-502 (benzo[g]quinoline) is the first non-ergot

dopamine agonist (7). It has been specifically designed as a selective D_2 agonist with little or no D_1 receptor agonist activity. Its potency has been estimated to be about 35-times greater than that of bromocriptine (8). In healthy volunteers the duration of its action indicates that the drug is suitable for once daily administration (9). In early studies in healthy volunteers and hyperprolactinaemic patients, no clinically significant adverse reactions or changes in safety parameters were observed (10-12). The reported adverse reactions were always mild or moderate and none of the volunteers or hyperprolactinaemic patients had to terminate treatment prematurely. Several of the hyperprolactinaemic patients in early studies with CV 205-502 had in the past shown resistance or experienced severe adverse reactions during treatment with bromocriptine or other commercially available dopamine agonists (13-14). This strongly suggested a more favorable adverse reaction profile of CV 205-502 as compared to other dopamine agonists. It was therefore decided to explore in a prospective, double-blind and randomized fashion whether the acute and long-term tolerability and safety of CV 205-502 would show a significant difference from that of bromocriptine.

MATERIALS AND METHODS

Forty-seven women with longstanding hyperprolactinaemia with or without a microprolactinoma were included in the study. Pretreatment serum prolactin levels were persistently >1500 mU/l (upper normal range is ≤800 mU/l, 36 mU/l = 1 ng/ml). They were otherwise healthy women between 18 and 47 years of age and all agreed to participate for a 24-weeks period, unless side effects or adverse reactions required premature discontinuation of treatment. The study protocol had been approved by the ethical committees of the participating hospitals and all women gave their written consent prior to entrance into the study after both oral and written information. The study was conducted according to the Tokyo amendment of the Declaration of Helsinki.

Thirteen women suffered from secondary amenorrhoea, 10 from oligomenorrhoea and 1 woman had a regular cycle despite hyperprolactinaemia. The remaining 23 patients discontinued their dopamine agonist therapy at least 1 month preceding the study and repeated prolactin measurements thereafter showed serum prolactin to be persistently above 1500 mU/l. Thirteen patients wanted to achieve pregnancy during the study. In all of them, three consecutive ovulatory cycles were monitored before mechanical contraception was stopped and conception was pursued. Table 1 shows pretreatment findings in the two study groups. It can be concluded that the randomization was successful.

All women received capsules of identical appearance in two packets, one for the morning and one for the evening intake, containing either CV 205-502, bromocriptine or a placebo. They all took two capsules a day, during breakfast and with a snack at bedtime. The starting dose for bromocriptine was 1.25

Table 1 Anamnestic and descriptive data of patients, randomized into the CV 205-502 group (CV) or Bromocriptine (BR) group

Item	CV	BR
No of women	23	24
Age (years, mean ± SEM)	31 8 ± 1 36	34 2 ± 1 37
Height (cm, mean ± SEM)	167 1 ± 1 25	164 8 ± 1 36
Weight (kg, mean ± SEM)	65 1 ± 2 36	62 4 ± 2 54
Infertility[a]	7	6
Galactorrhoea	10	5
Amenorrhoea[b]	7	6
Oligomenorrhoea[c]	4	6
Previous bromocriptine med	15	19
Microadenoma	9	8

[a]more than 1 year
[b]more than 6 months
[c]between 6 weeks and 6 months

mg at bedtime with a placebo morning capsule during the first 3 days, followed by 1.25 mg at breakfast and at night for the next 3 days (days 4-6). Thereafter bromocriptine 2.5 mg was taken twice daily. The starting dose of CV 205-502 was 0.025 mg at bedtime with a placebo capsule during the morning for the first 3 days, followed by 0.05 mg for the next 3 days (days 4-6) with thereafter 0.075 mg at bedtime. CV 205-502 treated women always took a placebo capsule during the morning. After 8 and 16 weeks the dose of bromocriptine or CV 205-502 could be adjusted according to the measured prolactin suppressant effect. CV 205-502 could be increased to 0.10 or 0.15 mg at bedtime; bromocriptine could be increased in a similar way to 7.5 mg by changing the evening capsule to one containing 5 mg bromocriptine or 10 mg changing both the morning and evening capsules to 5 mg. All medication packets were numbered and each patient received a number in correspondence with the number on the medication packages she could use. To guarantee the double-blindness of the study a change in dosage meant a change of both the packets containing morning and evening capsules.

Physical examinations, extensive blood and urine analysis and ECG evaluations were performed at baseline and repeated throughout the study at 4-week intervals. Serum prolactin, body weight, blood pressure and pulse rate (supine and standing) were also measured at 4-week intervals. Each individual patient was seen throughout the investigation period by the same investigator. At each visit the women were examined for the presence of galactorrhoea and questioned regarding the regularity of the cycle and the occurrence of adverse reactions by way of a questionnaire.

Serum prolactin was measured by use of commercially available radioimmunoassays (Farmos Diagnostica, Turku, Finland; Medgenix Diagnostics, Brussels Belgium). The upper limit of normal in menstruating women is 800 mU/l. All

other laboratory measurements (blood chemistry, haematology, urine analysis) were performed applying specific and sensitive standard laboratory procedures. All results are expressed as geometric mean values ± standard error of the mean (SEM), and the Wilcoxon signed-rank test was used for calculations of differences between the two groups.

RESULTS

Patient population

Two women were excluded from the study within 2 weeks from beginning of drug intake due to poor compliance, 1 in each group. Their data are completely excluded from evaluation. An additional woman in the CV 205-502 group had to be excluded due to violation of the protocol at 8 weeks. Up to week 8 of the trial her data are included in the analysis. An additional 5 women, 1 in the CV 205-502 group and 4 in the bromocriptine group, withdrew after week 4 and 4, 4, 4, 8 respectively, due to adverse reactions. Until withdrawal, their data are included in the analysis. Therefore, 21 patients in the CV 205-502 group and 20 in the bromocriptine group were available for evaluation throughout the first 8 weeks, 20 and 19, respectively, thereafter.

Serum prolactin concentrations

The mean serum prolactin profiles in the 2 treatment groups, calculated after the code was broken at 24 weeks, are shown in figure 1. In both groups a highly significant decrease in serum prolactin concentrations occurred within the first few weeks ($P < 0.001$) with mean prolactin levels well below the upper limit of normal thereafter in both groups. There was no significant difference in prolactin levels between the groups. After 8 weeks of treatment 17 (81%) of the 21 evaluable patients in the CV 205-502 group had normalized their serum prolactin levels. Serum prolactin levels of the 1 woman who withdrew from the study at 8 weeks because of adverse reactions were 130 mU/l at discontinuation. None of the remaining 4 women with elevated prolactin levels at 8 weeks normalized during the next 4 weeks despite a dose increase of CV 205-502. At 24 weeks, 2 of the remaining 4 women had normal serum prolactin levels with daily CV 205-502 doses of 0.150 mg. The remaining 2 women had persistently elevated concentrations of 1900 and 1700 mU/l, respectively, despite daily CV 205-502 doses of 0.150 mg, the highest dose allowed within the protocol.

In the bromocriptine treated group 14 (70%) of the 20 evaluable women at week 8 had serum prolactin levels within the normal range. Three women withdrew from the study at 4 weeks and 1 at 8 weeks due to side effects. The remaining 6 women had their bromocriptine dose increased to 7.5 mg. One

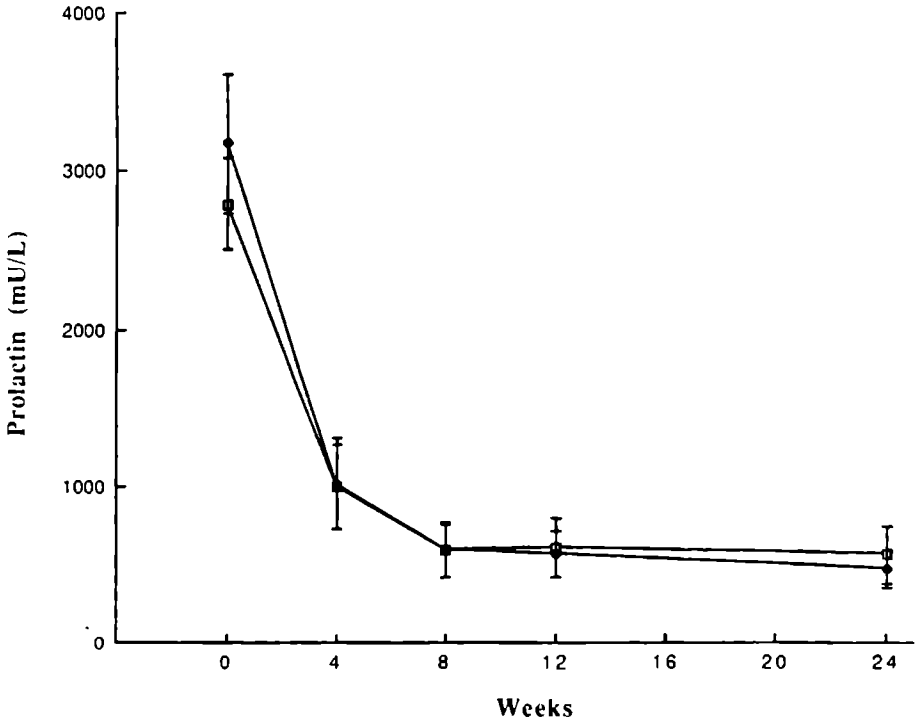

Figure 1. Serum prolactin levels (mean ± SEM) in CV 205-502 (closed diamonds) and bromocriptine (open squares) treated women.

reached normal serum prolactin concentrations at week 12, an additional 2 normalized between 12 and 24 weeks and 3 still had hyperprolactinaemia at 24 weeks, with values of 2900, 2200 and 1200 mU/l, respectively, despite a daily bromocriptine dose of 10 mg, the highest allowed within the protocol.

Menstrual cycle

Table 2 summarizes cycle characteristics previous to and during treatment. Thirty-two of the evaluable patients had dopamine agonist treatment until 1 month prior to this study, 21 of them were menstruating regularly. They continued to have regular menses throughout the study. Eight women had oligomenorrhoea. At 8 weeks only 4 patients had still oligomenorrhoea, and at 24 weeks all women still in the study, reported regular menstrual cycles. The remaining 3 women had amenorrhoea and developed a regular menstrual pattern at the end of therapy. The randomization in groups is listed in table 2.

Amenorrhoea. Seven women in the CV 205-502 group and 6 in the bromocripti-

Table 2 Cycle characteristics of the CV 205-502 and bromocriptine-treated groups at initiation of therapy and at 8, 12 and 24 weeks of treatment

	CV 205-502				Bromocriptine			
Week	0	8	12	24	0	8	12	24
No of patients	23				24			
excluded	1	1	1	-	1	3	1	-
evaluable	22	21	20	20	23	20	19	19
Amenorrhoea								
with[a]	1	1	1	-	2	-	-	-
without[b]	6	3	1	-	4	2	2	2
Oligomenorrhoea								
with[a]	3	2	-	2	5	1	-	1
without[b]	1	1	-	-	1	-	-	-
Regular								
with[a]	10	13	17	15	11	16	16	14
without[b]	1	1	1	1	-	1	1	1
Pregnancy				2				1

[a]with dopamine agonist treatment
[b]without dopamine agonist treatment

ne group were amenorrhoeic at initiation of therapy. In the CV 205-502 group 3 reported regular menstruations at 8 weeks and the remaining 4 were still amenorrhoeic. At 24 weeks all had menstruated, although 2 had oligomenorrhoea. Of the 6 amenorrhoeic women in the bromocriptine group, 2 responded with normalization and regular menstruation at 8 weeks. At 24 weeks only 2 women in this group remained still amenorrhoeic.

Oligomenorrhoea. At initiation of therapy 10 women were oligomenorrhoeic. The CV 205-502 group contained 4 of these patients. One was excluded after 4 weeks of treatment due to adverse reactions and an additional one after 8 weeks due to violation of the protocol. Both had still oligomenorrhoea. The remaining 2 women were still oligomenorrhoeic at 8 weeks, but developed regular cycles thereafter. In the bromocriptine group were 6 oligomenorrhoeic patients. One woman was also excluded due to adverse reactions after 4 weeks of treatment. Four women menstruated regularly at 8 weeks and the last one developed regular cycles shortly thereafter.

Regular menstrual cycles. One patient (CV 205-502 group) menstruated regularly at initiation of therapy and continued to do so while in the study. One woman in the bromocriptine group menstruating regularly developed oligomenorrhoea at the end of therapy despite normal serum concentrations of prolactin. Of the women still in the study at 24 weeks, therefore, 80% in the CV 205-502 group and 79% in the bromocriptine group were menstruating regularly.

Pregnancies

Thirteen patients (7 in the CV 205-502 group and 6 in the bromocriptine group) wanted to conceive, of whom 10 had regular ovulatory cycles within 2 months of treatment. After 3 ovulatory cycles had been recorded, 11 of them stopped mechanical contraception. Two patients conceived during treatment weeks 20 and 24, respectively. They both belonged to the CV 205-502 group and their prolactin concentration at conception had normalized, being 540 and 150 mU/l at dosages of 0.1 and 0.15 mg CV 205-502, respectively. A third patient conceived during treatment week 18 and belonged to the bromocriptine group. Her prolactin level was 100 mU/l and her dose 7.5 mg bromocriptine. During a 6-month open label follow-up period when all women received CV 205-502, an additional 4 women conceived, 3 who had started with CV 205-502 and 1 who had started with bromocriptine.

Galactorrhoea

At initiation of therapy, 15 women had signs of galactorrhoea; 10 (55%) in the CV 205-502 group and 5 (32%) in the bromocriptine group. In 13 of them galactorrhoea disappeared rapidly during treatment, and at 8 weeks only one patient in each group still had this complaint. At 24 weeks of treatment galactorrhoea had disappeared in all patients.

Tolerability

Five women discontinued treatment due to poor tolerability within the first 8 weeks, 4 in the bromocriptine group and one in the CV 205-502 group. Patients in the former group reported dizziness (2x), headache (1x) and nausea (2x) as reasons for withdrawal, whereas the patient in the latter withdrew from treatment due to nausea and headache. As mentioned earlier there were three additional dropouts, all beyond 8 weeks of treatment, due to poor compliance in two instances (one in each group) and one due to violation of the protocol (CV 205-502 group). Therefore 21 patients in the CV 205-502 group and 20 in the bromocriptine group were available for further evaluation concerning tolerability after 4 weeks. Table 3 summarizes the adverse reactions in the two groups. In general, the recorded adverse reactions were mild and often transient, especially in the CV 205-502 group. Most frequent adverse reactions in the CV 205-502 group were nausea and headache, whereas in the bromocriptine group besides these complaints, dizziness and obstipation were also recorded rather frequently. From week 8 onwards the dose could be increased, and this may have influenced the frequency of reported adverse reactions thereafter.

At 24 weeks of treatment, just before breaking the randomization code, all women still in the study, including the drop-outs, were asked to judge the overall

Table 3 Adverse reactions in CV 205-502 and bromocriptine treated women throughout the study period (one patient may have reported more than one complaint)

Group	CV 205-502				Bromocriptine			
Week	4	8	12	24	4	8	12	24
Complaint								
Nausea	12	4	2	-	7	4	3	1
Headache	6	2	-	1	3	2	2	3
Dizziness	3	2	1	3	4	4	2	1
Obstipation	1	1	-	-	5	2	1	1
Anorexia	1	1	-	-	2	1	-	-
Tiredness	-	-	-	1	2	4	-	-
Stuffy nose	-	-	-	-	2	-	-	-
Stomach pain	4	3	1	-	3	1	-	-
Total No of registered complaints	27	13	4	5	28	18	8	6
No of patients with complaints	18	10	3	5	16	9	6	5

tolerability of the treatment as very good, good, moderate or poor. In the CV 205-502 group 59% of the patients reported the tolerability to be very good, 32% to be good whereas one patient (5%) judged the tolerability as moderate and the last patient (5%) as bad. In the bromocriptine treated group these figures were, respectively, 46, 29, 8 and 17%.

Safety

At entry into the study all safety parameters were within normal limits in all of the patients. During the entire treatment period no clinically significant changes occurred in routine physical examinations, blood chemistry, haematology or urine analysis except for one woman in the bromocriptine group who had a significant increase in her CPK at 12 weeks of treatment due to an accident with muscle damage. The CPK value normalized rapidly thereafter. Neither could any significant effect on blood pressure be demonstrated in both groups nor were complaints indicating (orthostatic) hypotension mentioned. The ECG recordings did not change throughout the observation period except in two instances, one in each group, where clinically non-significant transient signs of atrioventricular blocks were seen. Both women had shown ECG recordings in the past with the same transient changes. Such findings are likely to be seen within any randomly controlled group when serial ECGs are recorded.

DISCUSSION

This study shows that CV 205-502 is at least as effective as bromocriptine in the normalization of serum prolactin in hyperprolactinaemic women Within the doses used, 81% of the patients in the CV 205-502 group had normalized their serum prolactin compared to 70% in the bromocriptine group This strong prolactin suppressant effect of 0 075 mg CV 205-502 administered once daily has also been shown in several open studies in hyperprolactinaemic women (9-14) The pharmacological action of this new compound is significantly longer than that of bromocriptine (11), allowing once daily administration This advantage increases the compliance with CV 205-502 From this study and from other dose finding studies (7,10,11) we therefore can conclude that once daily administration of CV 205-502 of 0 075 mg is at least as effective as 2 5 mg bromocriptine bid Although in this double blind study, the CV 205-502 dose of 0 075 mg was reached via stepwise titration similar to that generally used at the start of bromocriptine therapy, previous studies had documented that a starting dose around this level is well tolerated (10,13,14)

As expected, this study also convincingly demonstrates that once prolactin reaches normal values, gonadal function restores At the end of treatment all normoprolactinaemic women had regular menstrual cycles except for 1 woman in the CV 205-502 group who had oligomenorrhoea (despite normal prolactin levels) If restoration of gonadal function is the aim of treatment in hyperprolactinaemic women as it is in case of infertility, it can be postulated with great certainty that normal menstrual function will re-occur once normoprolactinaemia is reached (2,3,15) There was no difference between the two tested drugs in this regard Also, galactorrhoea often disappears rapidly while under treatment and, like the restoration of normal gonadal function, this is most likely linked to the control of the elevated prolactin rather than to the type of dopamine agonist used

The tolerability profile of CV 205-502 seems better than that of bromocriptine, which can be concluded from the following observations.

In the bromocriptine group 4 dropouts were recorded due to adverse reactions against only 1 in the CV 205-502 group When further analyzing the data, it appeared that 10 of the patients in the CV 205-502 group had shown intolerance to bromocriptine in the past Nine of these women tolerated CV 205-502 well, while the remaining one dropped out due to adverse reactions Four of these women had in the past shown resistance to bromocriptine up to the doses used in this study without normalization of prolactin During this study, 3 of them normalized while under CV 205-502 treatment whereas the fourth patient was the dropout with adverse reactions Similar observations have been made by others (16)

The adverse reactions mostly recorded in the CV 205-502 group were nausea, stomach pain, headache and dizziness Only in one instance these adverse reactions became so severe that drug intake had to be stopped Similar adverse reactions

also occur in bromocriptine-treated women but, in addition, a wider scale of side effects can be seen, like tiredness, obstipation, anorexia and stuffy nose. Finally, when the participating women were asked at the end of the study previous to breaking the code, how they had accepted the drug therapy, 90% of the CV 205-502-treated women judged the acceptability as good or very good versus 75% in the bromocriptine group. In our opinion this, indeed, indicates that the new drug has a better tolerability profile than bromocriptine and therefore widens the dose range in which it can be prescribed. Case reports have been published in which women intolerant or resistant to bromocriptine did respond to high doses of CV 205-502 with normalization of their serum prolactin levels (16).

In this short term study period of 6 months, none of the drugs gave rise to significant changes in the evaluated safety parameters. For bromocriptine this was as expected, since the drug has been widely used and has been recognized as very safe. Studies with CV 205-502 so far have also failed to demonstrate any hazard of this drug (12-14). There are, however, rather limited data on the safety of the drug during early pregnancy in humans although at present some 30 children have been born after exposure to CV 205-502. In animal experiments no toxic or teratogenic effects have been shown in the offspring (Personal communication Sandoz Ltd, Basle, Switzerland). This point has to be investigated very carefully during further studies with CV 205-502 and in infertile women it is recommended that drug intake should stop as soon as the menstrual period has been missed by more than 3 days.

In conclusion, the results from this double-blind study clearly show that CV 205-502 is highly effective in the treatment of hyperprolactinaemia, the adverse reaction profile is tolerable, with 90% of patients assessing tolerability as good or very good at the end of treatment. The once daily dose schedule is convenient and allows little or no interference of possible side effects with daily activities.

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CHAPTER 6

LACTATION INHIBITION BY THE NEW DOPAMINE AGONIST CV 205-502

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ABSTRACT

In an open pilot study with a parallel group design, 30 bottlefeeding women were randomly assigned in a two to one ratio to receive either the new dopamine agonist CV 205-502 or bromocriptine for lactation inhibition Ten women who intended to breastfeed served as normal controls

All treated women reached prepregnant prolactin levels within 72 h with once-daily 0 075 mg of CV 205-502 or twice-daily 2 5 mg of bromocriptine, at starting doses of 0 05 mg and 2 5 mg respectively Fifteen of the 20 women treated with CV 205-502 reported breast symptoms, 50% occurring on days 3 and 4 of treatment Three of the 10 women treated with bromocriptine had breast symptoms between days 2 and 28

Overall efficacy and tolerance in the two groups was very good Side effects did not differ between the groups, with the exception of pulse rate in the standing position, which was significantly higher in the bromocriptine treated group than in either the CV 205-502 group (P=0 02) or the breastfeeding group (P<0 01) The coagulation tests (fibrinogen, AT III, PTT and APTT) showed no significant differences between the three groups

INTRODUCTION

There are many reasons why puerperal lactation may need to be inhibited, social reasons being the most common (1-2). Effective suppression of puerperal lactation had long been a problem until the introduction of the dopamine agonist bromocriptine in the 1970's (3-6), but several recent reports have implicated bromocriptine in various side effects in the puerperium (7-10).

The non-ergot dopamine agonist CV 205-502 is an octahydrobenzo[g]quinoline (11) which has demonstrated strong prolactin lowering effects in various animals, in healthy volunteers and in hyperprolactinaemic patients (12-15). Approximately 80% of the hyperprolactinaemic patients treated during a dose-titration study, achieved normal prolactin levels with once daily doses of CV 205-502 between 0.05 and 0.10 mg (16). The drug has been generally well tolerated, and reported

adverse effects were transient nausea, sleepiness and headache during the initiation of therapy (14). Since studies so far indicate that the drug is safe (ECG recordings, physical and laboratory blood and urine tests) it was expected that the strong 24 h prolactin suppressant properties of CV 205-502 should offer an effective and well accepted alternative for use in inhibition of puerperal lactation.
Therefore it was decided to study prospectively the clinical and prolactin suppressant effects of a once-daily dose of CV 205-502 in the prevention of postpartum lactation. A parallel group received a twice-daily dose of bromocriptine (Parlodel®, Sandoz Ltd, Basle). The safety of CV 205-502 was assessed by way of standard laboratory blood tests, selected measures of coagulation and fibrinolysis and physical and ECG examinations. The assessment of vital signs, coagulation and fibrinolysis was also performed in the bromocriptine treated patients and in a control group of 10 normal women who intended to breastfeed.

MATERIALS AND METHODS

Study design

In this first study to test CV 205-502 in the suppression of postpartum lactation, an open model was chosen to examine two aspects of the suppression of postpartum lactation: (i) to find the optimal dose of CV 205-502 and to compare its effect with that of bromocriptine both clinically and on plasma prolactin levels; (ii) to assess the safety of CV 205-502 by means of ECG and complete laboratory urine and blood tests, including tests of coagulation and fibrinolysis. A two to one ratio was chosen to receive either CV 205-502 (20 women) or bromocriptine (10 women). The patients and investigative staff were aware of the treatment of each patient. Ten women who intended to breastfeed were selected to serve as normal controls for vital signs and tests of coagulation and fibrinolysis. The study had been approved by the ethical committee of the hospital and all women gave their written informed consent to participate.
All women had regular menstrual cycles previous to their pregnancies and had conceived spontaneously. They had no problems during the pregnancy and were delivered between 37 and 43 weeks gestation. None of the women used medication which could interfere with the administered dopamine agonists, and intake of oral contraceptives was to be delayed until day 42 postpartum.
The treatment was started within 24 h after delivery. In the CV-group, CV 205-502 was given as a daily oral dose at bedtime of 0.05 mg (day 1), 0.075 mg (days 2-14) and 0.05 mg (days 15-21). In the bromocriptine-group, bromocriptine was given twice daily 2.5 mg (days 1-14), followed by once daily 2.5 mg (days 15-21) to prevent rebound lactation (6). If breast tenderness or milk production was recorded at any time after day 4, the bedtime dose of CV 205-502 could be increased to 0.125 mg up to day 14 and a further dose increase of 0.05 mg daily could be given if necessary.

Assessment

The patients were visited for assessment on days 0 (day of delivery), 1, 2, 3, 4, 6, 9, 12, 15, 18, 22, 24, 28, 35 and 42 On these days blood samples were obtained to estimate prolactin (PRL) levels The women were questioned about breast symptoms (milk production, congestion and pain) and side effects The following rating scale was used none, mild, moderate (no treatment required) and severe (treatment required) The amount of milk secretion was classified as follows none, mild (few drops), moderate (spontaneous secretion) and severe (stream of milk) These daily observations were graded according to the severity and duration of the symptoms as follows very good, no symptoms or mild short-lasting symptoms (<24h), good, mild long-lasting symptoms (>24h) and/or moderate short-lasting symptoms (<24h), moderate, moderate long-lasting symptoms (>24h) and/or severe short-lasting symptoms (<24h), poor, severe long-lasting symptoms (>24h) The safety of CV 205-502 was tested by routine physical examination, ECG and laboratory tests (haemoglobin, platelets, leucocytes and differential count, urea, creatinine and liver enzymes) on days 0 and 42 Coagulation tests (fibrinogen, activated partial thromboplastine time (APTT), prothrombine time (PTT) and antithrombine III were performed on days 0, 1, 12 and 42 Pulse rate and blood pressure were recorded at each visit in the supine position and after 3 minutes' standing to examine the possible presence of orthostatic hypotension The Spectria competitive solid-phase RIA from Farmos Diagnostica (Turku, Finland) was used for measuring PRL (sensitivity 30 mIU/l and inter-assay variation 9%)

Statistics

The Wilcoxon rank sum test was used to analyse the PRL results and other laboratory findings Fisher's exact test was used to compare the clinical results. Differences with $P < 0.05$ were considered significant

RESULTS

Four women started to take oral contraceptives before day 42 post partum, two in the CV 205-502 group (days 15 and 26) and two in the bromocriptine group (days 22 and 30) When all data were examined including or excluding the findings or measurements in these four women, the results remained the same, so data from these women are included

The characteristics of the women in the three study groups are given in table 1, there were no significant differences between the groups.

Table 1 Descriptive data of each study group

Variable	CV 205-502 (n = 20)	Bromocriptine (n = 10)	Breastfeeding (n= 10)
Age (years) mean (SEM)	28 3 (0 8)	27 3 (0 9)	30 4 (1 1)
Parity			
primiparae	8	5	8
multiparae	12	5	2
Mode of delivery			
vaginal	18	8	8
cesarean	2	2	2
Gestational age at delivery (weeks)			
37	2	1	1
38	3	1	-
39	2	-	3
40	6	5	5
41	6	3	-
42	1	-	-
43	-	-	1

Prolactin

Figure 1 summarizes mean prolactin concentrations in the three groups: both CV 205-502 and bromocriptine suppressed prolactin to the normal prepregnant range (< 750 mU/L) within 72 h. Bromocriptine-treated women tended to normalize more rapidly. The calculated mean half life for prolactin suppression in the bromocriptine group was 0.59 (SD 0.43) and 0.87 (SD 0.33) in the CV-group (P=0.09). In both groups a rebound phenomenon occurred after withdrawal of the drugs on day 21. In the bromocriptine group also an increase of prolactin from day 14 onwards was obvious after dose reduction. From day 35, all prolactin measurements were within the normal range. The prolactin profile in breastfeeding women was quite different with a gradual decline until day 28, with clearly elevated levels thereafter. The initial period was characterized by fluctuating levels in each woman. Blood sampling for prolactin measurement was not related to time of breastfeeding.

Efficacy

Three of the 10 women in the bromocriptine group and 15 of the 20 women in the CV-group reported breast symptoms. In the bromocriptine group symptoms were recorded for 1 to 3 days. In the CV-group, six women had symptoms for 1 day, six had symptoms for 2 days, two had symptoms for 3 days and one had symptoms for 4 days. Although the women had moderate symptoms

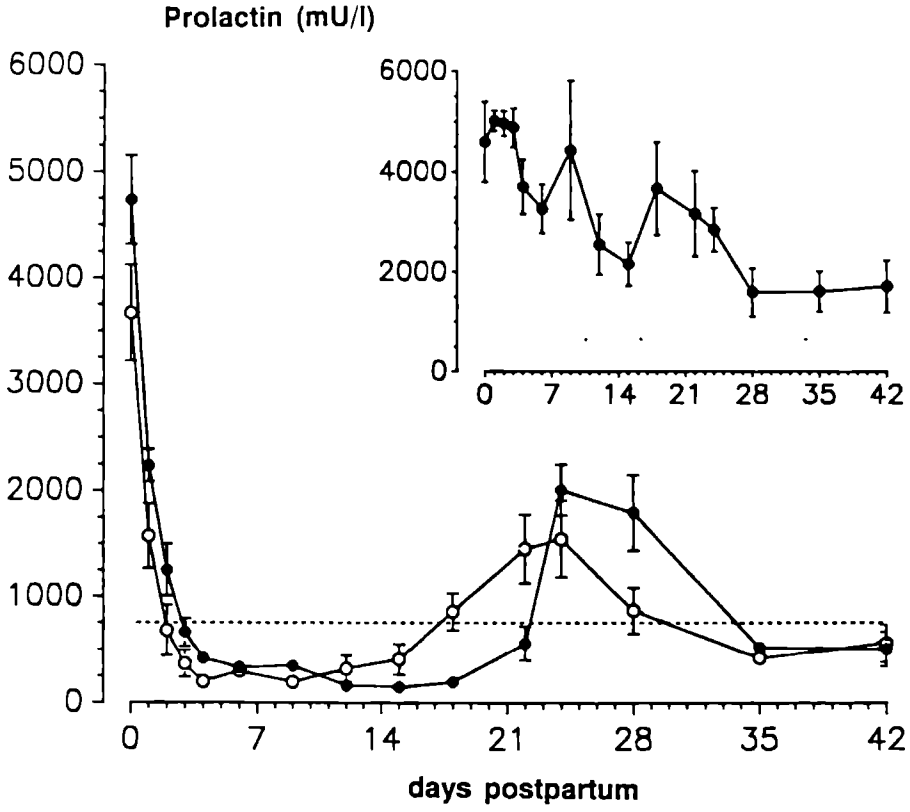

Figure 1 Mean serum prolactin (mIU/l ±SEM) values during CV 205-502 (-●-) and bromocriptine (-○-) treatment Inset mean serum prolactin (mIU/l ±SEM) values in the breastfeeding group

the dose was increased and the complaints disappeared. In one other woman the dose was increased after 3 days of increasing complaints. In the CV-group more than 50% of the complaints occurred during days 3 and 4 whereas in the bromocriptine group the complaints were much more spread out between days 2 and 28 No rebound lactation took place after cessation of medication. The final assessment of overall efficacy for the 20 women in the CV 205-502 group was very good in 12, good in 6 women, moderate in 1 and poor in one (figure 2). In the bromocriptine group 8 women graded there symptoms as very good and the other two as moderate. The difference between the groups was not significant (P=0.54).

Side effects

In both groups side effects were reported, mostly of mild intensity and none

of the participants withdrew from the study because of side effects. Figure 2 summarizes the overall tolerance and there was no significant difference between the two groups (P = 0.54). In the CV-group 10 of 20 women reported side effects: headache (4), dizziness (3), nausea (4), vomiting (1) and insomnia (1). One of these 10 women complained of nausea and vomiting on days 3 and 4, which resulted in interruption of treatment for one day (day 4). She was delivered by caesarean section and the complaints were attributed to the presence of bowel distension. Dizziness and nausea were reported at initiation of therapy whereas headache was reported even after cessation of medication by two women. Three of 10 women in the bromocriptine group reported side effects: headache (2), dizziness (2) and nausea (1). In this group also dizziness and nausea occurred at initiation of therapy.

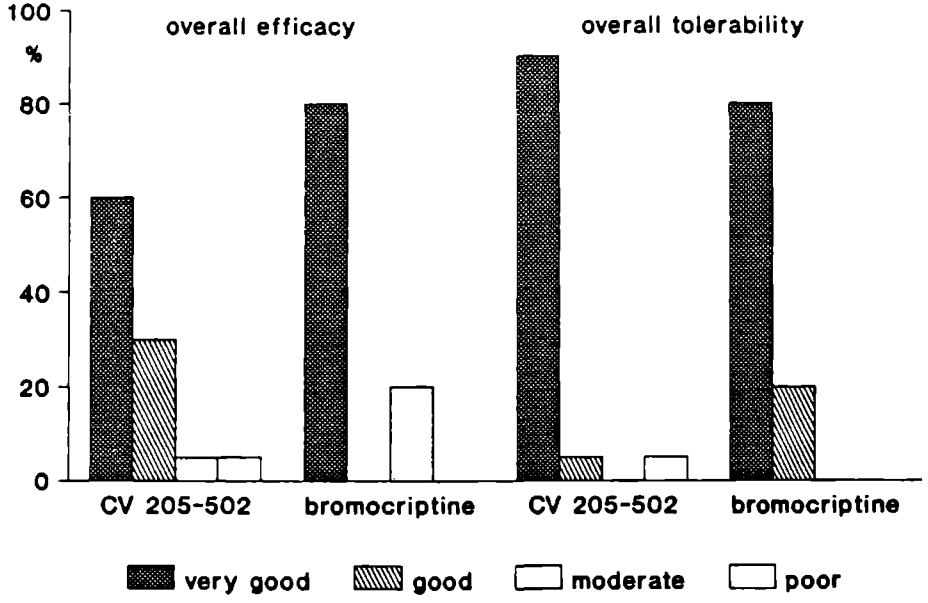

Figure 2. Overall efficacy and overall tolerance as judged by the investigator in the CV 205-502 and bromocriptine treated groups.

Safety

In the supine position blood pressure (systolic and diastolic) and pulse rate did not show significant differences between the three groups. After 3 min of standing blood pressure remained unchanged in all groups whereas pulse rate increased. There was no significant difference in the pulse rate on standing between the

breastfeeding control group and the CV-group (P=0 24), but the women in the bromocriptine-group had a significantly higher pulse rate (P<0.01) than the CV-group (P=0 02)

Table 2 summarizes the changes in coagulation and fibrinolysis variables. The values obtained on days 0 (before drug intake) and 42 are compared; the values on days 1 and 12 did not differ significantly from those on day 0 (all P-values >0 2) and they are not shown There was no significant difference between

Table 2 Comparison of coagulation and fibrinolysis tests on day 42 versus day 0 Number of measurements (n), mean difference (x) and standard error of the mean of the difference (SEM) are shown

	CV 205-502			Bromocriptine			Breastfeeding		
	n	x	SEM	n	x	SEM	n	x	SEM
Fibrinogen (g/l)	18	-1 06	0 16	7	-1 37	0 2	10	-1 28	0 33
AT III (%)	18	8 7	1 9	8	5 0	1 5	10	10 5	3 3
PPT (sec)	18	0 2	0 4	8	-0 4	0 4	10	0 0	0 4
APTT (sec)	18	4 8	1 4	8	2 3	1 8	9	3 9	1 7

the three groups on day 0 and day 42 The post partum period was characterized in all women by a decrease in fibrinogen (P<0 02) and an increase in anti-thrombine III (P<0 04), APTT tended to increase but this change was significant only in breastfeeding women (P=0.03). PTT remained constant.

The results obtained from routine haematology and blood chemistry in the CV-group did not show significant differences between days 0 and 42. The most persistent finding was a highly significant decrease of creatinine phosphokinase (CPK) in all women (day 0: mean 210 (SD 130) units, day 42: mean 70 (SD 80), P<0 01).

In the CV-group ECG recordings on day 0 were normal in 18 women and one woman had slight tachycardia with flattened T waves, on day 42 all women had normal ECG recordings. A full general examination on days 0 and 42 did not show any changes which could be attributed to the use of CV 205-502.

DISCUSSION

Previous studies have shown dopamine agonists like bromocriptine to be effective in the inhibition or suppression of lactation (17). In the present study bromocriptine showed the well known profile of rapid suppression of prolactin concomitant with nearly complete inhibition of mammary activity.

The new dopamine agonist CV 205-502 was very similar in its profile: rapid prolactin suppression and inhibition of mammary activity. The difference between these two drugs, which was not statistically significant, was the more rapid normalization of prolactin levels in bromocriptine treated women. This may explain why the women in the CV-group, who reported signs of mammary activity

tended to do so on days 3 and 4. This suggests that the initial dose of 0.050 mg of CV 205-502 was slightly too low and should be increased to 0.075 mg. Indeed 0.075 mg has been recommended as a starting dose in gynaecological patients suffering from symptomatic hyperprolactinaemia (16). After withdrawal of the drugs on day 21 a significant prolactin rebound release was obvious in both groups. In the bromocriptine group this rebound release already began on day 14 when the drug dose was decreased. The difference in the patterns of the two curves (figure 1): a sharper rise in the CV-group and a more flattened curve in the bromocriptine group, indicates that after acute inhibition of pituitary prolactin release, an easily releasable prolactin pool remains in the lactotrophs for at least three weeks (18-19). Despite this rebound release, however, no signs of rebound mammary activity were seen. Shorter suppression of prolactin has been reported to result in rebound lactation in a substantial percentage of women (6). The mammary gland after 3 weeks of prolactin suppression is less responsive to prolactin. An explanation for this may be the fact that around day 21 in dopamine agonist treated women, ovarian activity is restored, with many women actually experiencing their first ovulations during this period (20). High levels of circulating 17β-oestradiol, possibly in combination with progesterone, protects the mammary epithelium from the stimulating effect of prolactin (21).

In this study only mild side effects of headache, nausea, dizziness and insomnia were reported in some women in both groups except for one patient who suffered of bowel distension on days 3 and 4 after an abdominal delivery. These findings are in agreement with previous reports that postpartum women tolerate dopamine agonists very well (22).

Of great interest is the statistically significant increase in pulse rate seen in bromocriptine treated women compared with the CV-group and breastfeeding women although there were no significant changes in blood pressure. This may indicate that bromocriptine exerts a haemodynamic effect, which was absent following CV 205-502 treatment and in the breastfeeding women. This finding may be seen as a tendency to orthostatic hypotension in bromocriptine treated women which was counteracted by the increase in pulse rate. CV 205-502 treated women behave in this respect like breastfeeding women indicating that this drug has little or no influence on the cardiovascular system. This is in agreement with findings in volunteers and in hyperprolactinaemic patients in whom no influence on blood pressure and pulse rate was found (12-16).

There were no significant differences in changes in the clotting factors between the treated and control group. Few data have been published on changes in the coagulation and fibrinolysis systems post partum. The observed changes, similar in all three groups, with a decrease in fibrinogen and an increase in antithrombin III indicates that the hypercoagulability present during pregnancy (23), gradually disappears. Although it has been suggested that dopamine agonists could influence these indices unfavorably, this study clearly demonstrates that neither CV 205-502 nor bromocriptine influence coagulation and fibrinolysis. Also in the CV 205-502 treated women, no significant changes were observed

in routine haematology and blood chemistry aside from the highly significant decrease of CPK from day 0 to day 42 This is explained by the uterine muscle strain during delivery and by the involution of the uterus thereafter General physical examinations and ECG recordings in CV 205-502 treated women measured previous to and after treatment did not reveal any changes, also indicating the safety of CV 205-502 in postpartum patients

It can be concluded that CV 205-502 is as effective as bromocriptine in the prevention of puerperal lactation The drug has the advantage over bromocriptine that once daily administration is sufficient to produce normoprolactinaemia Although the number of patients in our study is small, the findings are in agreement with other reports suggesting that CV 205-502 is a safe drug The reported side effects were differed little, but in our opinion the observed difference in haemodynamic changes between bromocriptine and CV 205-502 treated women and lactating women, would favour the use of CV 205-502 Our data indicate that further studies are necessary to identify the optimal starting dose, 0 05 mg seems to be too low Therefore no definite conclusions on starting dose and safety of CV 205-502 in the indication of inhibition of lactation can be drawn with certainty from this study Further prospective trials are needed to answer these questions

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CHAPTER 7

GENERAL DISCUSSION AND CONSIDERATIONS

It was only during the late sixties and early seventies that the existence of human prolactin as a single and separate hormone next to human placental lactogen and human growth hormone was proven (Pasteels 1972, Friesen and Hwang 1973). Thereafter an explosion of publications has dealt with physiology and pathophysiology of prolactin in man (Nicoll 1974). Notwithstanding, the complete role of prolactin in many processes is still unsolved.

A very remarkable development was the fact that during the sixties ergot alkaloids like bromocriptine were shown to have prolactin lowering properties in several animal species (Berde and Schild 1978). It was postulated that this was also the case in man which indeed proved to be correct. The fact that bromocriptine or at that time known as CB 154 (Corrodi et al. 1973) was ready for clinical testing at the very moment that the first radio-immuno assays for prolactin determination became available, has certainly accelerated our knowledge regarding prolactin (patho)physiology. Although originally it was suggested that all patients suffering from hyperprolactinaemia could be treated efficiently with bromocriptine, we were to discover that this was not the case: a minority of patients will not respond with adequate prolactin suppression (Pellegrini et al. 1989). Furthermore, minor to severe adverse effects have been registered, nearly all specific to ergot derivatives. Basic research into the effects of ergot alkaloids at cellular level has taught us that stimulation of the D_2-dopamine receptor is critical in the process of lowering prolactin concentration (Ketabian and Calne 1979).
However, ergot alkaloids also tend to stimulate D_1-receptors and it is thought that many of the side effects occur through this stimulation (Ferrari et al. 1982). These effects consist mostly of nausea, dizziness and a tendency to orthostatic hypotension (Thorner et al. 1980). Unfortunately, bromocriptine has a rather short half life of approximately three hours which necessitates frequent drug intake to keep blood concentrations at therapeutic levels (Ho and Thorner 1988). The undulating concentration in itself may give rise to side effects as may the high concentrations reached in the stomach where dopamine receptors are present. It therefore became obvious that the development of a new dopamine agonist, with a more selective effect at the D_2-dopamine receptor level, would be of advantage in the treatment of hyperprolactinaemic patients.

Many such compounds have been tested and in this thesis some results are

presented of phase 2 and phase 3 investigations with 2 of the most promising new dopaminergic compounds: CQP 201-403 and CV 205-502.

Initially it was questioned whether patients suffering from hyperprolactinaemia should also be treated when there is no desire for pregnancy. At present however, it is generally agreed that hyperprolactinaemic subjects with a macro-adenoma of the pituitary gland (Molitch et al. 1985), women suffering from infertility due to hyperprolactinaemic amenorrhoea (Thorner and Besser 1977, Bergh 1989) and men suffering from impotence due to hyperprolactinaemia all need treatment. It has also become evident that hyperprolactinaemia (Franks et al. 1978) in the absence of macro-adenomas may give rise to unwanted situations such as severe bone loss in women due to their hypo-estrogenic state (Klibanski et al. 1980, Schlechte et al. 1983). It has also been queried as to whether or not elevated prolactin levels are a causative factor in the development of benign and malignant breast tumours and hyperlipidaemia (Nagasawa et al. 1981, Vorherr 1986, Pelkonen et al. 1982).
It seems therefore that the general consensus exists that hyperprolactinaemic patients should be treated continuously if the treatment is tolerated reasonably well. All these factors underlined the necessity to search for specific, well tolerated and safe dopamine agonists. Although bromocriptine itself has proven to be extremely safe (Weil 1986) with no long term serious effects on patient or child, the side effects have continued to be a problem in a substantial group of patients.

In our department which has a long tradition in clinical research within the field of prolactin and hyperprolactinaemia, we first studied the effectiveness, tolerability and safety of the new dopamine agonist CQP 201-402, in three dosages (0,01 mg, 0,02 mg and 0,03 mg). CQP, like bromocriptine is an ergot alkaloid derivative but it has a substantial longer half life (Grevel et al. 1986). The once a day administration of this drug showed a dose dependent prolactin suppression in all subjects as compared to placebo. All safety parameters measured during this study and during simular studies elsewhere, have indicated that further research with this compound could be carried out. However, its side effect profile was quite comparable to that of bromocriptine.

During our research with CQP 201-403, parallel studies were carried out elsewhere, mainly in Upsala in Sweden, with the compound CV 205-502 (Rasmussen et al. 1987, Venitikou et al. 1987). When the data from all these studies were compared, both preparations seemed equally effective in their prolactin suppression capacity and all safety parameters remained normal. However, the side effect profile of CV 205-502 was clearly better than that of CQP 201-403, and therefore Sandoz, Basle, Switserland, decided to further develop CV 205-502. From a theoretical point of view this last compound has several advantages: it is a completely computer designed molecule in which the pharmacologists have tried to develop a specific D_2-dopamine receptor agonist without or with only minor

D_1-receptor stimulating properties (Nordmann et al. 1985, Closse et al. 1988). In contrast to the other compounds, this is not an ergot alkaloid derivative. Like CQP CV has a half life sufficiently long to justify a once daily administration. Initial experiments on hyperprolactinaemic volunteers with dosages varying between 0,01 and 0.09 mg once a day showed a dose dependent prolactin suppression with normalisation of prolactinlevels when the higher dosage was used (Gaillard et al. 1986) . In the healthy volunteer studies with women and men without hyperprolactinaemia CV 205-502 showed a significantly better tolerance as compared to CQP and it was therefore to be expected that this new drug would be of advantage for hyperprolactinaemic subjects intolerant to bromocriptine.

When synthetizing the drug, the pharmacologists used as basis the linear benzo[g]quinoline and substituted this with ergoline. CV205-502 is therefore an octahydrobenzo[g]quinoline (Nordmann et al. 1985). To show the D_2-dopamine receptor stimulation several studies were carried out in many in vitro models using both rat and human pituitary cell cultures containing prolactin producing cells from adenomas (Gaillard et al. 1989). These studies like others also focused on the interaction between the D_1 and D_2-dopamine receptors demonstrating the more specific potency to stimulate the last one as compared to bromocriptine.

The first experiments in human volunteers focused on tolerability and safety (Gaillard et al. 1986). Early studies also measured the possible effect of the new compound on pituitary production and release of other hormones than prolactin: TSH, FSH, LH, ACTH and growth hormone (Brue et al. 1989). Eventually the release of both FSH and LH changed but this is due to the reactivation of gonadal function and is not specific for the compound. However, in acute experiments a slight but significant increase in growth hormone secretion could be demonstrated. This was also the case in our study. This effect on growth hormone seems to be common for all dopamine agonists (Vance et al. 1987). In contrast to other dopamine agonists compounds, the effect of CV 205-502 on growth hormone secretion is reproducable in time within the same subjects (Miell et al. 1990). As treatment goes on and becomes chronic the growth hormone response to provocative stimuli normalizes. In this respect our study is in agreement with those carried out by others during the same period.

During acute CV 205-502 administration the pituitary prolactin response to an acute TRH provocation is practically identical in healthy, normoprolactinaemic volunteers as compared to hyperprolactinaemic women. This is interesting since it has been postulated that dopamine agonists would also block this response to TRH. Vemer has shown the same in his studies in puerperal women (Vemer 1979). It may very well be that during chronic experiments the prolactin response to TRH becomes blocked. The reasoning would then be that in an acute experiment

the dopamine agonist would block the release of prolactin while prolactin is still stored within the cell. TRH, when stimulating prolactin release through different receptors will then bring about release of the stored prolactin in the cell. It is only during chronic dopamine treatment that the cell content of prolactin diminishes (Pasteels 1977). Once this has occurred no further prolactin release in response to TRH can take place.
Several phase 3 studies carried out in a prospective, randomized and double blind fashion have compared the effect of bromocriptine and CV 205-502 in hyperprolactinaemic women. However, one of the first and most extensive of these is the study reported in this thesis. From this it can be concluded that CV 205-502 is at least as effective as bromocriptine in its prolactin lowering properties. Once normal prolactinaemia is restored both compounds are equally effective in restoring the gonadal function and inhibition of galactorrhoea.

As was to be expected, the tolerability of CV 205-502 is better than that of bromocriptine. Although in our study this is not clearly demonstrated from the number of drop outs in the two groups, the fact that 9 out of 10 patients who in the past had shown intolerance to bromocriptine, had accepted CV 205-502 very well, which strongly argues in favour of the new compound. Furthermore, three of four patients who had been considered resistant to bromocriptine responded to the new drug with normalization of their prolactin concentrations. After our study several reports in agreement with this finding have appeared in the literature (Homburg et al. 1990, Newman et al. 1989).

Although not mentioned in the publications presented in this thesis, several casuistic reports from our own group of patients could be added to emphasize the broader therapeutic range of CV 205-502 with respect to prolactin suppression: one woman who did not tolerate bromocriptine in amounts of 20 mg a day and who did not respond to this dose with normalization of her prolactin level, tolerated CV 205-502 without side effects at a dose of 1.1 mg and it was only when this dose had been reached that prolactin started to normalize. This was followed by a rapid restoring of gonadal function and the occurrence of a pregnancy. We, like others, can add several comparable cases to prove that from a clinical point of view CV 205-502 is of extreme value (Vance et al. 1989, Khalfallah et al. 1990, Barnett et al. 1990, Serri et al. 1990).

It must be underlined however, that also during CV 205-502 therapy side effects may occur, especially at the initiation of treatment. From our studies it seems justified to conclude that these side effects are related to the initiation of therapy, to the moments when dose increases take place and to the speed by which prolactin concentrations decrease.

In our studies like in others an overall tolerance of approximately 90% or more is confirmed during CV 205-502 intake and this is encouraging (Rasmussen et al. 1988).

In contrast to the studies during the days when bromocriptine was introduced, modern trials have much more extensive safety parameters built into their protocols with the administration of the new drugs This of course has also been the case during experimental CV 205-502 intake None of these safety parameters which could show a drug relationship have changed during or after drug administration All studies in the literature so far agree on this point (Rasmussen et al 1988, Homburg et al 1990) However, we must realize that the clinical experience with this new drug is approximately 5 years at the moment and we should continue to be cautious This is especially true for women seeking treatment for infertility

From a theoretical point of view it was not expected that the pregnancy rate in CV 205-502 treated women who responded with normalization of their ovarian function during treatment would be different from that in bromocriptine treated women Indeed studies so far have shown that once ovarian function has restored, a normal fertility rate is to be expected Of importance is the fact that animal experiments have shown no toxic or teratogenic effects of the new compound in dosages far above those needed to influence prolactin release

Until now 35 pregnancies have been registered The outcome has been reported to be normal without suspicion of specific abnormalities related to drug intake It goes however without saying that extreme caution has to be maintained regarding pregnancy outcome Women suffering from hyperprolactinaemia and infertility who use this new compound should be advised to apply mechanical contraception until a regular cycle has reappeared Thereafter a pregnancy may be started and the intake of CV 205-502 should be discontinued as soon as a missed period by a few days is noted The course and the outcome of pregnancy must be recorded in the same way as in hyperprolactinaemic women treated with bromocriptine for infertility (del Pozo and Darragh 1977, Griffith et al 1978, Weil 1986) To the best of our knowledge the same guideline has been used in all centres where the new compound has been prescribed in phase 3 and phase 4 trials

As was to be expected CV 205-502 is very effective in the inhibition of puerperal lactation As with bromocriptine (Rolland and Schellekens 1973) it brings about a rapid prolactin decrease with a prepregnant range of prolactin concentrations within 24 to 48 hours post partum In our study we have prudently started with a low dose of the new compound with neglect to the fact that the puerperal women during the first or second day of drug intake tolerate the drug generally well A starting dose of 0,075 mg seems advisable After withdrawal of CV 205-502, a prolactin rebound occurred in most women comparable to the experience with bromocriptine treated women Several of these women also complained of "rebound" breast symptoms Therefore, as for bromocriptine, the new compound has to be taken for three weeks to ensure that rebound breast

activity does not occur. Preferably however, depot preparations should be made available similar to those with bromocriptine (Parlodel^{R} LA and Parlodel^{R} LAR).

Of great interest is the difference in pulse frequency in the two groups of puerperal women receiving either bromocriptine or CV 205-502. The last group did not show any difference with the control group of breastfeeding women whereas bromocriptine treated women showed a significant increase in their pulse rate after three minutes of standing. We suggest that the explanation for this difference must be based on the more specific D_2 dopamine receptor stimulating properties of CV 205-502 as compared to bromocriptine with at the same time less D_1 dopamine receptor stimulation (Flückiger et al. 1990). The increase in pulse frequency is explained as a tendency to orthostatic hypotension which is compensated by an increase in pulse rate.

Until recently there has been a marked shortage of studies on coagulation and fibrinolysis in puerperal women (Beller et al. 1982). We have had the opportunity to compare several parameters within these two systems in CV 205-502 treated women, bromocriptine treated women and lactating women. Despite the differences between the dopamine treated women and the lactating women with regard to the restoring of gonadal function, no differences in the measured parameters could be observed between the three groups. Although it has been suggested that during dopamine treatment a hypercoagulability could occur, we have not been able to confirm this. With respect to both coagulation and fibrinolysis it is safe to say that the two systems remain in balance during dopamine agonist treatment without any sign of hypercoagulation.

After review of our own studies regarding the clinical testing of new dopamine agonists and also after a thorough review of the literature concerning these compounds as it has emerged during the last few years, we think that the following conclusions can be drawn.

CQP 201-403 is a potent dopamine agonist with a half life which allows a once daily administration. Although the tolerability is reasonable, it compares in this respect with bromocriptine. The side effects are similar to those of all ergot alkaloid derivates.

CV 205-502 is the first non ergot alkaloid dopamine agonist showing strong prolactin lowering properties. In this respect it is comparable with bromocriptine. During exertion of its action it does not influence the acute pituitary response of TSH, ACTH, FSH or LH after intravenous administration of releasing hormones. The acute effect on growth hormone secretion is comparable with that of other dopamine agonists, it is reproducable and it disappears eventually during chronic administration.

The profile of side effects of CV 205-502 is considerably better than that of bromocripti-ne. This explains why the new compound is better tolerated. As a consequence the "therapeutic window" of CV 205-502 is significantly greater than that of bromocriptine It allows so called dopamine agonist resistant patients to be treated adequately.
CV 205-502 is as effective as bromocriptine in the inhibition of puerperal lactation.
In puerperal women bromocriptine brings about a significant increase in pulse frequency after 3 minutes of standing. This increase is absent in CV 205-502 treated- and lactating- women The explanation for this increase is thought to be a compensatory mechanism for orthostatic hypotension.

The changes that take place in the coagulation and fibrinolysis systems in puerperal women are similar in dopamine agonist treated women (bromocriptine and CV 205-502) and lactating women.

All safety parameters so far indicate that CV 205-502 is a safe drug.

Hyperprolactinaemic women treated with CV 205-502 for reasons of infertility should be followed prospectively during and after pregnancy in order to further investigate the safety of CV 205-502 with respect to offspring.

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SUMMARY

In this thesis the new dopamine agonists CQP 201-403 and CV 205-502 are being studied and their efficacy, tolerance and safety in a group of 142 hyperprolactinaemic women is reported.

Chapter 1 gives a survey of the literature. It mentions the history of the hormone prolactin, its endocrine regulation patterns and its workingmechanisms. The pathophysiology of hyperprolactinaemia and methods of treatment are briefly reviewed.

Chapter 2 describes the effects of CQP 201-403, a propyl-ergolin, in a group of 24 hyperprolactinaemic women. In a double blind study three different dosages of CQP 201-403 are compared with a placebo. A dose-dependent decrease of serum prolactin is observed with a once daily drug administration. With the exception of prolactin, none of the other hormonal parameters studied are changed significantly. Tolerance is moderate to good and regarding safety parameters, no changes that could be drug-related have been observed. Further studies with CQP 201-403 have been discontinued for industrial political reasons, but also since the tolerance of the second compound is judged to be better.

Chapter 3 deals with a prospective randomized, double blind placebo controlled study with CV 205-502, a octahydrobenzo[g]quinoline, in 12 hyperprolactinaemic patients.

A combined pituitary challenge test with GnRH, TRH, CRH, and GHRH is carried out in two groups of patients, before and after 4 weeks of treatment with 0.05 mg of CV 205-502 or a placebo. In the CV treated group a 64% decrease of serum prolactin is observed. The prolactin response to CV 205-502 is blunted after TRH administration, but a tendency towards normalisation is shown after 4 weeks of treatment. The reason for this is assumed to be the initial block of prolactin secretion from the lactotropic cells, which precedes the inhibition of synthesis in these cells.

The response of GH, TSH, LH, ACTH and cortisol does not change. FSH, however, shows a significant decrease after 4 weeks of CV 205-502 administration. This is explained by an increase of oestradiol due to the restoring ovarian function. No changes in the hormonal parameters is observed in the placebogroup.

Chapter 4 describes the efficacy, tolerance and safety of CV 205-502 in increasing dosages (maximum 0.150 mg) during a 12 month treatment period in 41 patients. The previously described efficacy of this drug is confirmed, as well as the high to excellent degree of tolerance and safety during a long period of treatment. Patients who have shown bad tolerance towards bromocriptine in the past, responded better to CV 205-502 in this study and treatment could be continued.

In *Chapter 5* CV 205-502 is compared with bromocriptine (Parlodel®). After

randomization a double blind study is undertaken in 47 women during a period of 24 weeks. Both drugs show very good and comparable efficacy. Inthe course of treatment, tolerance however, is better in the CV 205-502 group. The degree of normalisation of the ovarian function and the disappearance of galactorrhoea is equally observed.

Chapter 6 contains the open comparison of inhibition of lactation in a CV 205-502 and a bromocriptine treated group next to a control group of lactating women. Besides, changes in coagulation and fibrinolysis systems are studied. In the group of 20 women who are taking 0.075 mg of CV 205-502 daily, a normoprolactinaemic level is reached within 72 hours. Slight breast symptoms occur in 15 women, notably on treatment day 3 and 4. In the bromocriptine group of 10 women, a prolactin decrease is reached to the same extent within the same time. In 3 of these women breast symptoms are registered between day 2 and 28. Tolerance in both groups is very good. Only the pulse frequency in standing position is significantly increased in the bromocriptine treated group compared to the CV treated or the control group. This may be explained by a stronger D_1-receptor stimulation by bromocriptine thereby inducing orthostatic hypotension that is compensated by a higher pulse frequency. Blood coagulation studies in the 3 groups show no significant differences.

In *chapter 7* the preceding studies are evaluated and compared existing literature. The following conclusions can be drawn:

- CQP 201-403 is an effective dopamine agonist with a half life which permits a once daily administration. Tolerance and side effect profile are comparable to those of the known derivatives of ergot alkaloids like bromocriptine.
- CV 205-502 is the first non ergot alkaloid dopamine agonist. It gives a strong prolactin decreasing effect which is comparable to that of bromocriptine. It exerts its action without influencing the pituitary-thyroid, pituitary-ovarian or pituitary-adrenal axis. The influence on acute GH secretion is similar to that of other dopamine agonists.
- The side effect profile of CV 205-502 is better than that of bromocriptine. Consequently CV 205-502 has a larger therapeutic window.
- CV 205-502 is as effective as bromocriptine regarding inhibition of lactation. A significant increase in pulse frequency measured after 3 minutes in standing position during the use of bromocriptine is explained as a compensation-mechanism for orthostatic hypotension. The changes in the coagulation and fibrinolysis systems which occur normally in puerperal women, are present to the same exent in the groups who use the dopamine agonists studied and the group of lactating women.
- Measured safety parameters indicated that CV 205-502 a safe drug.
- Women with hyperprolactinaemia, who are treated with CV 205-502 for reasons of infertility, should be monitored closely during and after their pregnancies as should their off-spring in order to elucidate the safety of CV 205-502 with relation to mother and child.

SAMENVATTING

In dit proefschrift worden de nieuwe dopamine agonisten CQP 201-403 en CV 205-502 bestudeerd, waarbij vooral aandacht besteed wordt aan de effectiviteit, tolerantie en veiligheid bij 142 vrouwen met een hyperprolactinaemie.
Hoofdstuk 1 betreft een overzicht van literatuur gegevens. In eerste instantie belicht het de geschiedenis van het hormoon prolactine, daarna volgt een bespreking van de endocriene regulatie patronen en werkingsmechanismen. De pathofysiologie en behandelingsmethoden van hyperprolactinaemie, tenslotte, worden kort uiteengezet.
Hoofdstuk 2 beschrijft de effecten van CQP 201-403, een propyl-ergoline, in 24 vrouwen lijdende aan hyperprolactinaemie. In deze dubbel blinde studie worden drie doseringen CQP 201-403 vergeleken met een placebo. Er wordt een dosisafhankelijke prolactine verlaging waargenomen bij inname eenmaal per dag. Behalve de prolactine spiegel worden geen van de andere bestudeerde, hormonale parameters beïnvloed.
De tolerantie is redelijk tot goed en er treden geen veranderingen in de waarnemingen betreffende veiligheid op, die aan het middel moeten worden toegeschreven. Om bedrijfspolitieke redenen en vanwege de geconstateerde betere tolerantie van CV 205-502 werd afgezien van nadere studies met CQP 201-403.
Hoofdstuk 3 beschrijft een prospectieve, dubbel blinde, gerandomiseerde, placebo gecontroleerde studie met CV 205-502, een octahydrobenzo[g]quinoline, bij 12 hyperprolactinaemische patiënten.
In twee groepen van 6 patiënten wordt bij aanvang en na 4 weken behandeling met 0,05 mg CV 205-502 of een placebo, een gecombineerde hypofyse belastingstest met GnRH, TRH, CRH en GHRH uitgevoerd.
In de CV groep wordt een daling van de prolactine spiegel van 64% waargenomen. De reactie van prolactine na TRH toediening is verminderd voorafgaande aan CV 205-502 toediening, maar toont een trend tot normalisatie na 4 weken behandeling. Een reden hiervoor moet worden gezocht in de, in eerste instantie, optredende blokkade van de secretie van prolactine uit de lactotrofe cel, voorafgaande aan de remming van de synthese. De reacties van GH, TSH, LH, ACTH en cortisol veranderen niet. FSH echter toont een significante daling na 4 weken behandeling met CV 205-502. De verklaring hiervoor moet worden gezocht in de stijging van E_2 ten gevolge van een herstellende ovariële functie. In de placebogroep kunnen geen veranderingen in de hormonale parameters worden vastgesteld.
Hoofdstuk 4 is een beschrijving van de effectiviteit, tolerantie en veiligheid van CV 205-502, bestudeerd tijdens de behandeling van 41 patiënten gedurende 12 maanden, met oplopende doseringen tot een maximum van 0,150 mg CV

205-502. De reeds eerder beschreven goede effectiviteit van dit geneesmiddel kon worden bevestigd, evenals de goede tot uitstekende tolerantie en veiligheid gedurende langdurige behandeling. Patiënten die in het verleden werden behandeld met bromocriptine (Parlodel®) en daarbij een slechte tolerantie vertoonden reageerdenin deze studie beter op CV 205-502 en konden derhalve doorbehandeld worden.

Hoofdstuk 5. In deze dubbel blinde studie wordt uiteindelijk CV 205-502 met bromocriptine vergeleken. Na randomisatie worden 47 vrouwen met een hyperprolactinaemie verzocht, gedurende 24 weken óf CV 205-502 óf bromocriptine in te nemen.

Van beide medicamenten wordt een grote en vergelijkbare effectiviteit vastgesteld. De tolerantie blijkt echter in de loop van de behandeling in het voordeel van CV 205-502 uit te vallen. Het herstel van de ovariële functie en het verdwijnen van de galactorrhoea wordt in gelijke mate waargenomen.

Hoofdstuk 6 tenslotte behelst een open studie waarbij het lactatieremmend vermogen van CV 205-502 wordt vergeleken met dat van bromocriptine. Daarnaast is de bloedstolling en de veranderingen hierin onderwerp van studie. Een groep van vrouwen die borstvoeding geven dient hierbij als referentie. De groep van 20 vrouwen die CV 205-502 gebruiken in een dosering van 0,075 mg, bereikt binnen 72 uur normale prolactine waarden. Bij 15 vrouwen treden geringe tekenen van stuwing op, met name op dag 3 en 4 van inname. In de bromocriptine groep van 10 vrouwen wordt in gelijke mate en tijd een prolactine daling bereikt. Bij 3 van hen worden eveneens geringe tekenen van stuwing geregistreerd tussen dag 2 en 28. De tolerantie is in beide groepen zeer goed. Slechts de polsfrequentie in staande positie is in de bromocriptine groep significant hoger dan in de CV groep of de controle groep. De verklaring hiervoor berust waarschijnlijk op een sterkere D_1-receptor stimulatie door bromocriptine waardoor een neiging tot orthostatische hypotensie wordt geïnduceerd. Deze orthostatische hypotensie zou dan worden gecompenseerd door een hogere polsfrequentie. De testen betreffende coagulatie tonen in de drie groepen geen significante verschillen.

In *Hoofdstuk 7* worden de voorafgaande studies geëvalueerd aan de hand van bestaande literatuur.

De volgende conclusies kunnen worden getrokken:

- CQP 201-403 is een effectieve dopamine agonist, met een halfwaarde tijd die een toediening eenmaal per dag toelaat. De tolerantie en het profiel van bijwerkingen zijn gelijk aan de bekende ergot alkaloïden derivaten, zoals bromocriptine.
- CV 205-502 is de eerste non-ergot alkaloïde dopamine agonist. Het bezit een sterk prolactine verlagend effect, welke vergelijkbaar is met die van bromocriptine, zonder invloed uit te oefenen op de hypofyse-schildklier, -ovarium of -bijnier as. De invloed op de acute GH-secretie is vergelijkbaar met die van andere dopamine agonisten.
- Het profiel van bijwerkingen van CV 205-502 is gunstiger dan dat van

bromocriptine. Een consequentie hiervan is dat de therapeutische breedte van CV 205-502 groter is dan dat van bromocriptine.

- CV 205-502 is even effectief als bromocriptine voor wat betreft lactatieremming. Wel bestaat er een significante stijging van de polsfrequentie stijging tijdens bromocriptine gebruik, gemeten na 3 minuten in staande positie. Een aannemelijke verklaring lijkt te zijn dat het als compenserendmechanisme voor een neiging tot orthostatische hypotensie dient. De veranderingen, die optreden in de bloedstolling en fibrinolyses bij vrouwen in het puerperium, zijn in gelijke mate aanwezig bij hen die de onderzochte dopamine agonisten gebruikten als bij vrouwen, die borstvoeding geven.
- Alle gemeten parameters betreffende veiligheid geven aan dat CV 205-502 een veilig geneesmiddel is.
- Om de veiligheid van CV 205-502 met betrekking tot moeder en kind nader te bestuderen, is het noodzakelijk dat zowel de vrouwen, die om reden van infertiliteit hiermee behandeld worden, als hun kinderen tijdens en na de zwangerschap frequent worden gecontroleerd.

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CURRICULUM VITAE

De schrijver van dit proefschrift werd in 1952 in Oss geboren. In dezelfde stad werd in 1971 het eindexamen HBS-b afgelegd. Na een enerverende studentetijd behaalde hij in 1979 het artsdiploma aan de Rijksuniversiteit te Utrecht.
Na een jaar van enthiousiasme op de afdelingen Chirurgie en Gynaecologie & Obstetrie van het Diaconessenhuis te Naarden (Dr. A. Koch, Drs. R. Dik) werd in 1981 de opleiding tot vrouwenarts in het Catharina Ziekenhuis te Eindhoven (Dr. J.A.M. van Wyck) aangevangen. In 1984 vervolgde hij zijn opleiding in de kliniek voor Obstetrie & Gynaecologie van het St. Radboud Ziekenhuis te Nijmegen (Prof. Dr. T.K.A.B. Eskes en Prof. Dr. R. Rolland). In 1986 volgde inschrijving in het specialisten register als vrouwenarts.
Tot 1991 bleef hij verbonden aan het St. Radboud Ziekenhuis. Aanvankelijk als arts-onderzoeker, de laatste 3 jaar echter als staflid. Daarnaast vervulde hij, in de periode 1988 tot april 1991, part-time werkzaamheden en waarnemingen in respectievelijk het Diaconessenhuis te Naarden, Fertiliteits Centrum Oost te Nijmegen en het Diaconessenhuis te Meppel.
Sinds april 1991 is hij werkzaam in de maatschap der vrouwenartsen in het Twenteborg Ziekenhuis te Almelo.

Stellingen

behorende bij het proefschrift
"New dopamine agonists and hyperprolactinaemia"

1. De dopamine agonist CV 205-502 is een aanwinst in de therapeutische mogelijkheden voor patiënten lijdende aan hyperprolactinaemie.
(dit proefschrift)

2. De therapeutische breedte van CV 205-502 is groter dan die van bromocriptine.
(dit proefschrift)

3. Het geconstateerde verschil in polsfrequentie, gemeten na drie minuten staan, bij kraamvrouwen tijdens inname van bromocriptine danwel CV 205-502, strookt met de theorie dat bromocriptine meer D1-receptor stimulerende eigenschappen bezit dan CV 205-502.
(dit proefschrift)

4. Het innemen van dopamine agonisten in het kraambed beïnvloedt de fysiologische veranderingen niet, die optreden in bloedstolling en fibrinolyse post partum.
(dit proefschrift)

5. Het is billijk, dat van een candidaat leerling-verpleegster eenige algemeene ontwikkeling wordt gevraagd.
(P.E.G. van der Heijden, thesis 1934)

6. In de soms fel gevoerde discussie omtrent het al of niet geven van borstvoeding wordt weinig aandacht besteed aan het positieve effect dat lactatieremming kan hebben op het ontstaan van een goede band tussen vader en kind.

7. Indien moedermelk conform de normen, gesteld in de warenwet, wordt beoordeeld op het voorkomen van dioxiden, zou het niet mogen worden verkocht.

8. In de meeste gevallen geldt in de obstetrie, in tegenstelling tot in de psychiatrie: je kunt beter gescheurd dan geknipt zijn.

9. Een goede omloop is nooit weg.

juni 1991

P.F.M. van der Heijden